REMARKS

Favorable reconsideration of this application in view of the amendments and remarks to follow and allowance of the claims of the present application is respectfully requested.

In the Office Action dated June 14, 2005, Claims 1-3, 5-12, 14, 21 and 22 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. More specifically, the Examiner alleges that the amendment to Claims 1 and 15, filed November 4, 2003, to include "R is a C3-C6 cycloalkyl group, which is optionally substituted with a straight or branched C1-C6 alky group", does not find support in the original disclosure, and thereby is considered introduction of new matter into the present application.

Applicants submit that the amendment to Claims 1 and 15, filed November 4, 2003, to include "R is a C3-C6 cycloalkyl group, which is optionally substituted with a straight or branched C1-C6 alky group", is an amendment to correct an obvious error that does not constitute new matter because one skilled in the art would not only recognize the existence of the error in the specification, but also recognize the appropriate correction.

It is common knowledge in the biomedical field that modern drug discovery focuses on the search of the "pharmacophore", i.e., the group of atoms in a compound which are responsible for the biologic and pharmacologic action of the compound. In fact, the pharmaceutical industry has been routinely utilizing the methodology of structure-activity relationship (SAR) for many years to identify chemical structures that could have desirable inhibitory effects on specific targets and have low toxicity. SAR is a means by which the effect of a compound on an animal can be related to its molecular structure. This type of relationship may be assessed by considering a series of individual molecules and making gradual changes to

them, noting the effect upon their biological activity of each change. Based on the SAR studies, scientists often conclude a drug discovery research project with a general formula for the compounds indicating the characteristics of the pharmacophore. Thus, it is understood to one skilled in the art that a patent disclosing novel compounds and the medical use thereof provides both a general formula that characterizes the pharmacophore and certain preferred examples upon which the general formula is based.

The present invention is directed to novel ureido-pyrazole derivatives showing cdk/cyclin kinase inhibitory activity. In the Summary of the Invention section, the specification presents the general formula (I) with the definition of R as a C1-C6 alkyl, aryl or arylalkyl group that is optionally substituted. However, in the Detailed Description of the Invention section, the specification emphasizes that preferred compounds of the present invention of formula (I) are those wherein R is a C3-C6 cycloalkyl (lines 24 and 28, page 10). Further, the specification recites more than 100 examples of preferred compounds at pages 11-14. Nearly 90 out of these examples are compounds of formula (I) wherein R is a C3-C6 cycloalkyl. Since it is well known in the art that the general formula in a patent is based upon the preferred examples and thereby encompasses them, one skilled in the art, in view of the disclosure in the Detailed Description of the Invention section, would readily ascertain that the general formula (I) includes an obvious error as it omits certain definitions for R.

Further, there is a proviso at the end of the definition of formula (I) in the Summary of the Invention section and Claim 1. As you know, the proviso is a commonly used drafting method in pharmaceutical patents to further narrow, not to augment, the scope of a general formula. The proviso at the end of the definition of formula (I) recites "when n is 0 and R2 is hydrogen, R is a C3-C6 cycloalkyl". However, the definitions of R prior to the proviso do not refer to the R group as a C3-C6 cycloalkyl. In view of the proviso and the recitation of R

being a C3-C6 cycloalkyl in the Detailed Description of the Invention section, one skilled in the art would readily recognize that "C3-C6 cycloalkyl" is the inadvertently omitted definition for R.

Thus, in view of the disclosure of the present application as a whole, one skilled in the art would not only ascertain that the general formula (I) has an obvious error of omission, but also recognize that the inadvertent omission is the definition of R as a C3-C6 cycloalkyl. Therefore, applicants submit that the amendment to Claims 1 and 15 to include a C3-C6 cycloalkyl group, is a correction of an obvious error, and thereby does not introduce any new matter.

Claims 1-3 and 5-14 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. More specifically, the Examiner alleges that in order to practice the claimed methods of treating cell proliferative disorders, one skilled in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Applicants submit that the specification contains sufficient information regarding the subject matter of the claims as to enable one skilled in the art to make and use the claimed methods of treating cell proliferative disorders without undue experimentation.

The present invention relates to novel ureido-pyrazole derivatives showing cdk/cyclin kinase inhibitory activity and the use thereof in treating cell proliferative disorders associated with an altered cell dependent kinase activity. The hallmark of cancer cells is the uncontrolled and dysregulated proliferation. Since cell-dependent kinases (cdk) are known to regulate cell proliferation, the direct inhibition of cdk/cyclin kinase activity can restrict the unregulated proliferation of tumor cells.

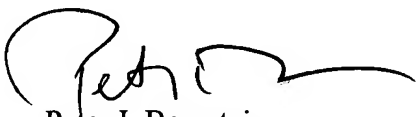
The present application not only defines the chemical structures of compounds of formula (I), but also provides processes for preparing those compounds with detailed reaction

conditions (pages 14-23 and Examples). The specification further delineates pharmacological protocols as to the dosage, host, and mode of administration for using compounds of formula (I) in the treatment of cell proliferative disorders (pages 23-27). It is notable that the specification recites that the compounds of formula (I) are active as cdk/cyclin inhibitors as they gave positive results when tested according to the procedure described therein (lines 9-10, page 23) and all compounds showing inhibition more than 50% were further analyzed in order to study and define the kinetic-profile of inhibitor through Ki calculation (lines 3-4, page 24). In view of such detailed description and the high level of the skill in the art, applicants submit that one skilled in the art would be able to practice the full scope of the present invention without any undue experimentation.

The rejections under 35 U.S.C. §112, first paragraph, have been obviated, therefore reconsideration and withdrawal thereof is respectfully requested.

Thus, in view of the foregoing amendments and remarks, the application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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(54) Title of the Invention: Method of preparation of a hydrogel

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(56) Cited Literature
Public Patent Bulletin S44-5332 (1969)
Public Patent Bulletin S48-35719 (1983)

(57) Scope of Patent Claims

1. A method for the preparation of a water-insoluble hydrogel that is characterized by the fact that, when preparing a hydrogel comprising a high-molecular weight copolymer containing hydroxyl groups and carboxylate groups in the molecule, saponification is caused for a copolymer consisting of 20~80 mole % of a vinyl ester component and 80~20 mole % of an acrylic or methacrylic acid ester component in the presence of an alkaline catalyst and a solvent,

under conditions where said copolymer does not dissolve, with the saponification being 50 mole % or more of the vinyl ester and 30 mole % or more of the acrylic or methacrylic acid ester.

2. The method of preparation recorded in Claim 1 that is characterized by the fact that the copolymer consisting of a vinyl ester component and an acrylic or methacrylic acid ester component a spherical item obtained by the suspension polymerization method.

Detailed Explanation of the Invention

The present invention relates to a method of preparation of a hydrogel having an ability to absorb a large amount of water.

In recent years, as the application of hydrophilic polymer materials to the medical industry, the food industry or agricultural fields has progressed, water-insoluble and hydrophilic or water-absorbing polymeric materials in particular have come to be employed for a variety of uses such as separation and refining materials such as the various membranes and carriers for liquid chromatography, enzyme supporting materials, cultures for microorganisms or plants, and medical materials such as contact lens and covering of sutured places, or for uses involving a capacity for water absorption and water retention.

Among these uses, particularly in the usage fields which make utilize the capacity for water absorption and water retention, it is desirable that the polymer materials possess absorb as great an amount of water as possible in a short period when they are brought into contact with water.

As methods for the preparation of polymeric materials that take such uses as their purpose, such methods as the crosslinking of a water soluble polymer with a crosslinking agent, the modifying of a water soluble polymer into a water-insoluble one by partial substitution of the hydrophilic groups with hydrophobic ones, and other methods are known of, and up to now there have been proposed several materials which are made of natural or synthetic polymer substances, such as the crosslinked products of polyethylene oxide, polyvinyl pyrrolidone, sulfonated polystyrene, or sodium polyacrylate, cellulose derivatives, and the saponified products of starch-acrylonitrile graft copolymers.

However, except for the saponified products of starch-acrylonitrile graft copolymers, the water-absorbing ability of these items is small, and thus they are unsatisfactory as water-absorbent materials. In addition, even in the case of the saponified products of starch-acrylonitrile graft copolymers, even though various improvements have been added to the process of their preparation there are still many problems from the standpoint of practical use, for example, the method for preparing them is relatively burdensome, and in the even that they are used in hydrated state over a long period of time there is the possibility that the starch component will rot and the gel structure will be destroyed.

As a result of the extensive examination with attention accorded to the status quo described above, the present inventors previously discovered the fact that a hydrogel with extremely high water absorption could be obtained by drying from a moderately hydrated state the water-soluble copolymer salt obtained by saponifying a copolymer containing vinyl ester and ethylene unsaturated carboxylic acid or a derivative of this, and they applied for a patent.

The characteristic of said previous invention lies in the fact that not only are the above-mentioned copolymer saponified products modified into water-insoluble materials without any treatment with a crosslinking agent, but also that the copolymers obtained after that quickly swell up in water, and they moreover possess a capacity to absorb an extremely large volume of water as much as several hundred times their own weight.

The result of these further improvements concerning the method for preparing the hydrogel comprising the above-mentioned copolymer group was that the present inventors discovered a method for preparing a water insoluble and moreover highly water absorbent hydrogel, not by way of a special gelation (or insolubilization **[sic]**) process but rather simply through a saponification process alone, from a copolymer comprising a vinyl ester and an acrylic acid (or methacrylic acid) ester as the starting material.

In other words, the present invention (1) provides a method of preparation of a spherical hydrogel that is characterized by the fact that, when preparing a hydrogel comprising a high-molecular weight copolymer containing hydroxyl groups and carboxylate groups in the molecule, saponification is caused for a copolymer consisting of 20~80 mole % of a vinyl ester component and 80~20 mole % of an acrylic acid (or methacrylic acid) ester component in the presence of an alkaline catalyst and a solvent, under conditions where said copolymer does not dissolve, with the saponification being 50 mole % or more of the vinyl ester and 30 mole % or more of the acrylic acid (or methacrylic acid) ester; and (2) in the method of preparation of a hydrogel in accordance with the above-mentioned method, saponification is carried out for the copolymer composed of the spherical vinyl ester and acrylic acid (or methacrylic acid) obtained by preparation by suspension polymerization.

As far as the method of the present invention is concerned, not only has the process of preparing the hydrogel been simplified, and thus extremely advantageous in the event that it is implemented industrially, the hydrogel obtained subsequently possesses the following characteristics: superior transparency, no coloration and ordinarily a water absorbing capacity of 10 times and more of its own weight; it is stable over a long period of time even in a state where it has absorbed a 1,000 times as much water [as its own weight]; and its strength is also great.

Copolymers comprising vinyl ester and acrylic acid (methacrylic acid) ester and the methods for preparing these are already well known, and in addition the obtainment of a water soluble copolymer by saponification of said copolymer is also well known (for example, *Kobunshi Kagaku* **[*Polymer Chemistry*]**, volume 7, page 142, 1950).

However, the preparation of a water insoluble and moreover highly water absorbent hydrogel by a method like that of the present invention has not been known. In addition, said copolymer saponification product has been known as simply the reformed product of polyvinyl alcohol, but its being used for an extremely highly water absorbent **[TN: wrong character in the text here.]** hydrogel that is the purpose of the present invention has not been known up to now.

It is possible to prepare the copolymer composed of vinyl ester and acrylic acid (or methacrylic acid) ester used for the present invention by any of the well-known methods for this. In other words, the method is selected as appropriate based on the polymerization mode, for example, it is synthesized by radical polymerization employing such polymerization initiating

agents as the bar oxide group such as d-*t*-butyl bar oxide, benzoyl bar oxide, etc., the persulfate group like ammonium persulfate, the azo compound group like azobisisobutyronitrile, etc. Solution polymerization, emulsion polymerization, suspension polymerization, etc., are applied as the polymerization modes, but the suspension polymerization method is employed for the purpose of obtaining a spherical hydrogel possessing a particle diameter between 10 μ and 1,000 μ.

The composition of said copolymer starting material exerts a great influence on the gel formability of the hydrogel obtained by means of the present invention and its water absorption capacity. In other words, when the acrylic acid (or methacrylic acid) ester component in said copolymer is too small not only is the water absorption capacity too small but a water insoluble gel cannot be obtained; moreover, when it is on the contrary too great there is a tendency for the gel strength in a highly water absorbent state to decline markedly.

Therefore, it is necessary for the proportion of the acrylic acid (or methacrylic acid) ester component in said copolymer that serves as the starting material generally to be within a range of 20 to 80 mole %.

Moreover, the preferred range in order to obtain a hydrogel whose water absorption capacity and hydrated gel strength are both superior is 30 to 70 mole %. In addition, it is preferable that the molecular weight of said copolymer starting material for the purpose of obtaining the hydrogel that constitutes the purpose of this invention be comparatively large. If this is expressed for the sake of convenience by the limiting viscosity (η) in a benzene solution at 30° C., ordinarily [η] will be 1.5 and above.

As the vinyl ester used for the preparation of said copolymer starting material, one may mention as examples such things as vinyl acetate, vinyl propionate and vinyl stearate, but ordinarily it is preferable to use vinyl acetate. Moreover, as the acrylic acid (or methacrylic acid) ester, one may mention as examples such things as the methyl, ethyl, n-propyl, iso-propyl, n-butyl and t-butyl esters of acrylic acid or methacrylic acid, but methyl acrylate in particular is preferred.

The highly water absorbent hydrogel that is the purpose of the present invention is obtained by saponifying the above-mentioned copolymers in the presence of an alkali catalyst and a solvent, under conditions in which the copolymers do not dissolve.

As the solvents used for the saponification reaction, one can mention alcohols and alcohol-water mixed liquids. According to the method of the present invention, the above-mentioned copolymer starting material is saponified in a state wherein the copolymers swell up in these solvents and disperse in them, but even if the degree of saponification is the same the gel formability and the water absorption will differ depending on the solvent used. For example, when the saponification reaction is performed with a water-alcohol mixed fluid whose composition is varied, generally the volume of water absorbed by the hydrogel obtained increases as the volume of water in the mixed fluid increases, but if the volume of water exceeds a certain proportion it is not possible any more to obtain a gel possessing water insolubility and moreover high water absorbance as per the present invention.

The amount and composition of the saponification solvent differs somewhat depending on the components and composition of the copolymer starting material composed of vinyl ester and acrylic acid (or methacrylic acid) ester, but ordinarily the amount of the saponification solvent falls within a range of 300 to 10,000 parts by weight to 100 parts by weight of said copolymers, and its composition, that is, the mixing proportions of water in the alcohol-water mixed fluid, falls within a range of 0.01 to 40 weight percent, and preferably a range of 5 to 30 weight percent.

As the alkali catalyst used for the saponification reaction, the well-known alkali catalysts are used, but in particular alkali metal hydroxides such as sodium hydroxide and potassium hydroxide are preferable. The saponification usually terminates between 1 and 10 hours in a temperature range between 20° C and 80° C, but the following point is particularly important in those cases where it is implemented according to the present invention. In other words, as far as the method of the present invention is concerned, when saponification is carried out under conditions like those described above, it is necessary to maintain the conditions whereby the copolymers do not dissolve in the saponification solvent at every stage of the saponification reaction. The above-mentioned copolymer starting material is insoluble in water, and on the other hand its solubility in alcohol is caused to differ depending on its composition. For example, in the case of a vinyl acetate methyl acrylate copolymer, in the event that the methyl acrylate component is small it is readily soluble in methanol, and when the methyl acrylate content becomes greater it becomes harder to dissolve in methanol. However, even in the latter case the solubility increases a good deal by heating. Therefore, when the present invention is implemented, it is to start the saponification at a low temperature so that the above-mentioned copolymer is not caused to dissolve at the time of the start of the saponification reaction, and then raise the temperature after the saponification reaction has progressed for some time and it has reached a state where it will not dissolve in the solvent.

On the other hand, the saponification reaction progresses even if water or a solvent in which water is the chief component is used for the saponification solvent, but in this case the copolymer dissolves in water as the saponification reaction progresses, and therefore a hydrogel like that intended by the present invention cannot be obtained.

When the present invention is put into effect, there are no particular restrictions on the shape of the copolymer starting material before saponification. By using a copolymer starting material having a spherical, fibrous, powdered or any other form one might wish in accordance with the purpose involved, it is possible to obtain hydrogels having the forms that correspond to each of these respectively. However, the embodiment preferred in particular at the time of implementation of the present invention is the method for preparing a spherical hydrogel.

It is necessary for the hydrogels that constitute the purpose of the present invention to include at least a hydroxyl group and a carboxylato group in the molecule. Therefore, the degree of saponification may be in range wherein the above-mentioned conditions are satisfied, but in order to make it water insoluble and to obtain a hydrogel possessing a high degree of water absorbance, for example, in the case of putting into effect the invention with a copolymer composed of vinyl acetate and methyl acrylate as the starting material, it is preferable that the degree of saponification of the vinyl acetate component of said copolymer be 50 mole % and

above, and still more preferably 90 mole % and above, and that of its methyl acrylate component be 30 mole % and above, and desirably 70 mole % and above.

As for the carboxylato group contained in the hydrogel obtained by the method described above, the alkali substance used for the saponification reaction catalyst has become a salt forming substance, but it is possible to vary its salt form by the well-known methods. For example, a hydrogel with an alkali metal salt form can be transformed into an organic amine salt by the ion exchange method, and by putting the saponification reaction into effect in the presence of 2 or more kinds of alkali substance it is possible to make it into a hydrogel with two or more salt forms. As conventional salt forming substances, on may mention such examples as alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; ammonium hydroxide; mono-, di- and tri-methylamine; mono-, di- and tri-ethylamine; mono-, di- and tri-isopropylamine; mono-, di- and tri-ethanolamine; mono-, di- and tri-isopropanolamine; N, N-dimethylethanolamine; N, N-dimethylisopropanolamine; N, N-diethylethanolamine; N, N-diethylisopropanolamine; N-methlethanolamine; N-methylisopropanolamine; N-ethylethanolamine; cyclohexylamine; benzylamine; aniline; pyridine; and other organic amines.

When the hydrogel that constitutes the present invention is made into an alkaline earth metal salt form such as magnesium, calcium, etc., its water-absorbing capacity declines markedly, and they are not suitable for the purposes as highly water absorbent gels, but in the event that they are made into mixed salts with the above-described kinds of salts it is also possible to employ multivalent metal salt forming substances.

The hydrogel constituting the present invention obtained by the method described above ordinarily possess as noted at the outset the capacity to absorb 10 times or more its own weight in water, but in the event that the water to be absorbed contains another substance, this water absorption capacity generally varies depending on the type and the amount of that substance. For example, with respect the capacity to absorb water pH differs, it possesses maximum absorption capacity for water whose pH is in the area of 8 to 11, and in such a case it can absorb water 500 times or more its own weight. Moreover, as the pH value deviates from this range the water absorption capacity declines, and in particularly the decline of water absorption capacity is marked within a pH range of 5 or below. However, the water absorbing capacity recovers completely when a hydrogel immersed in an acidic fluid is reimmersed in an alkali fluid. In addition, when a salt like NaCl is added to a gel that has absorbed water to a high degree it possesses such properties as releasing a large amount of water. In other words, it exhibits the reversible change of water absorption -- water release depending on the pH and the salt concentration of water.

In this manner, the hydrogel constituting the present invention is employed as a particularly optimal water absorbent material in those cases where water whose pH falls in a range of 5 to 12 is being absorbed, and the water absorption capacity can be varied by changing the composition and components of the copolymer starting material, the degree of saponification, and moreover the composition of the saponification solvent.

In addition, the hydrogel constituting the present invention is not only employed as a material that causes only water to be absorbed, but is also useful as an absorbent material for other liquids. For example, in the event that the salt form of the copolymer is finally an organic

amine salt, it possesses superior absorption capacity even for mixed liquids composed of an organic solvent like water-alcohol, water-acetone, and water, and therefore it is also possible to obtain a hydrogel that possesses a variety of absorption capacities depending on the selection of the salt form of the copolymer.

The hydrogel constituting the present invention as described above is equipped with the following advantages. In other words, first of all the hydrogel is transparent, there is not much coloring, and moreover there is almost no toxicity as would be easily inferred from the molecular structure that composes them, and therefore it is anticipated that it can be used without obstacles in those usage fields involving contact with the human body like various hygienic materials, for example disposable diapers, tampons, sanitary cotton, bandages, napkins, etc. Second, there is no fear of the gel rotting even when it is used for a long time in a hydrated state, and due to this it is optimal for various industrial uses, for example, as a separation agent for the water in oil and as other dehydrating agents and drying agents, or as a water retaining agent for plants and soils, or for other uses requiring water absorption and water retention. Third, the hydrogel is prepared extremely readily industrially, and not only is it particularly optimal in the event that a spherical hydrogel is used as a variety of carriers but it can also be molded into a variety of shapes depending upon the intended use, for example, after a fibrous or spherical hydrogel is crushing the gels in a water absorbent state it can be made into a film shape by the **[illegible; one character means "flow"]** method.

The present invention will be illustrated in more detail with reference to the following working examples, but the present invention is not limited in any way by these.

The water absorption rate or absorption rate in the working examples is expressed as follows:

> Water absorption rate/absorption rate = gel weight after absorption divided by dry gel weight

Working Example 1

0.5 g of benzoyl peroxide as a polymerization initiator was added to 60 g of vinyl acetate and 40 g of methyl acrylate, this was dispersed in 300 ml of water containing 3 g of partially saponified polyvinyl alcohol as a dispersion stabilizer and 10 g of NaCl, and suspension polymerization was carried out at 65° C for 6 hours. The methyl acrylate content of the copolymer obtained was 48 mole %, and its limiting viscosity in benzene at 30° C was 2.10

Next, 8.6 g of the above-mentioned copolymer was suspended in a saponification fluid containing 200 g of methanol, 10 g of water and 40 ml of 5N NaOH, the temperature was raised to 65° C after the saponification reaction was carried out at 25° C. for 1 hour, and then the saponification reaction was carried out for 5 hours. After the saponification reaction concluded, the reaction product was thoroughly washed with methanol, after which 6.8 g of a spherical dry saponified product with a particle diameter of 20 μ to 200 μ was obtained by drying under decompression.

The saponification degree of said saponified product was 98.3 mole %, and it possessed strong absorption of -- $C00^-$ at 1,570 cm^{-1} in the infrared absorption spectrum.

The spherical saponified product obtained in this manner was insoluble in water and it quickly swelled up in water, and its water absorption rate for de-ionized water was 750 g/g.

In addition, the transparency was excellent and it moreover possessed superior gel strength in a state where 750 g/g of water was absorbed, and in addition it was stable while maintaining the spherical gel form over a long period of time in excessive water.

Working Example 2

The spherical hydrogel obtained in working example 1 was added to excessive water, diluted sulfuric acid was added to it, and the pH was set at 3 and below. The hydrogel at this time shrank markedly, and it precipitated after a time. Next, this precipitate was isolated, and after it was thoroughly washed with water it was dried under decompression.

This isolated product maintained its spherical shape, but the absorption of $-COO^-$ had already disappeared for its infrared absorption spectrum, and instead of this it possessed a strong absorption of carbonyl, which suggests the presence of an acid and an ester across 1700 to 1800 cm^{-1}.

The above-mentioned isolated product was suspended in water, and tri-ethylamine was added to it. The product began to swell while maintaining its spherical form unchanged as the triethylamine was added.

After this system was left overnight, with the pH maintained at approximately 10 by addition of triethylamine, the excessive water was removed by filtering, and a spherical dried hydrogel was obtained once again by causing the gel in a swollen state to shrink by placing it in a large quantity of isopropanol and then drying it under decompression.

Strong absorption of $-COO^-$ appeared once again for the infrared absorption spectrum for this hydrogel, thereby suggesting that the form is of triethylamine salt.

The spherical triethylamine salt form hydrogel obtained in this manner is insoluble not only in water but also in methanol, water-alcohol mixed fluids, etc., and moreover it possessed superior absorption capacity (Table 1).

Table 1

Liquid being absorbed	Absorption ability (g/g)
Water	400
Methanol	95
Water-methanol mixture (water content 20%)	260
Water-ethanol mixture (water content 20%)	150

Water-isopropanol mixture (water content 20%)	45

Working Example 3

After an acetone solution of a vinyl acetate/methyl acrylate copolymer, with a limiting viscosity at 30° C in benzene of 1.95 and a methyl acrylate component of 51 mole %, was spun, it was cut and short fibers 10 mm long and 10 μφ in diameter were obtained.

Next, 8.6 g of said short fibers was dispersed in a saponification liquid composed of 200 g of methanol, 15 g of water and 40 ml of 5 N NaOH, and after a saponification reaction was carried out at 25° C for 1 hour the temperature was raised to 65° C and the saponification reaction was carried out for another 5 hours.

After the saponification reaction concluded, 7.1 g of a fibrous saponified product was obtained by thoroughly washing the reaction product with methanol and drying it under decompression.

The saponification degree of said saponified product was 97.5 mole %, and it possessed strong absorption of $-COO^-$ at 1570 cm^{-1} in the infrared absorption spectrum.

Said fibrous saponified product was insoluble in water and it quickly swelled up in water, and the water absorption rate for de-ionized water was 1,100 g/g, it maintained its fibrous gel shape in excessive water, and it was stable for a long period of time.

(H2)

PREPARATION OF HYDROGEL

Patent number:	JP57128709
Publication date:	1982-08-10
Inventor:	TATEGAMI YOSHIHARU; others: 03
Applicant:	SUMITOMO KAGAKU KOGYO KK
Classification:	
- international:	C08F20/04; C08F2/32; C08F22/02
- european:	
Application number:	JP19810015239 19810203
Priority number(s):	

Abstract of **JP57128709**

PURPOSE:To obtain a granular or spherical hydrogel of high water absorption having a sufficient gel strength, by the reverse phase water-in-oil type suspension polymerization of an alpha, beta-unsaturated acid (alkali metallic salt) with a specific hydrocarbon oil (fat) as an anti-tack agent.

CONSTITUTION:An alpha, beta-unsaturated acid (alkali metallic salt) monomer, e.g. (meth)acrylic acid (Na salt) is subjected to the reverse phase water- in -oil type suspension polymerization in a medium, e.g., n-hexane, with a hydrocarbon oil (fat), e.g. liquid paraffin, cottonseed oil, soybean oil or lard, having a boiling point above the drying temperature of the recovery system of a hydrogel, preferably 50 deg.C or more higher than the drying temperature and a melting point below the separating operation temperature of the hydrogel from the solvent, preferably 20 deg.C or more lower than the separating operation temperature. The anti-tack agent may be added before or during the polymerization or at a suitable time after the completion of the polymerization.

EFFECT:Special pulverizing treatment is not required, and the method is simple and economical.

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⑲ 日本国特許庁 (JP)　　⑪ 特許出願公開

⑫ 公開特許公報 (A)　　昭57—128709

⑤1Int. Cl.³	識別記号	庁内整理番号	⑬公開 昭和57年(1982) 8月10日
C 08 F 20/04			
2/32		7102—4 J	発明の数 1
22/02			審査請求 未請求

(全 8 頁)

⑤4ヒドロゲルの製造法

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㉒出　　願 昭56(1981) 2月3日
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明　細　書

1. 発明の名称

ヒドロゲルの製造法

2. 特許請求の範囲

1．α、β—不飽和カルボン酸モノマーまたは／およびそのアルカリ金属塩を油中水滴型の逆相懸濁重合法によつて製造するヒドロゲルの製造法において、粘着防止剤としてヒドロゲルの乾燥温度以上の沸点及びヒドロゲルと溶媒の分離操作温度以下の融点を有する炭化水素油または／および油脂を用いることを特徴とするヒドロゲルの製造法。

2．粘着防止剤がヒドロゲルの乾燥温度より50℃以上高い沸点及び分離操作温度より20℃低い融点の炭化水素油または／および油脂であることを特徴とする特許請求の範囲第1項記載のヒドロゲルの製造法。

3．炭化水素油または油脂が流動パラフィン、綿実油、大豆油、ナタネ油、ヤシ油、液体ロウ、ヘットまたはラードであることを特徴とする特許請求の範囲第1項記載のヒドロゲルの製造法。

3. 発明の詳細な説明

本発明は多量の水を吸収し保持する能力を有する高分子材料であるヒドロゲルの製造法に関する。

更に詳細には粒状または球状のヒドロゲルを特別の粉砕処理をせずして、経済的で簡便な方法により製造する方法を提供することにある。

近年、親水性高分子材料の医療産業、食品工業あるいは製造分野への利用が進むにつれて、特に水不溶性でかつ膨水性または吸水性を有するヒドロゲルが各種のメンブランや液体クロマト担体などの分離精製材料、酵素、固定担体、微生物や植物の培地、コンタクトレンズや綿合都被覆などの医療用材料あるいは吸水性や保水性を利用する種々の用途に用いられるようになつた。

これらの用途のうち、特に吸水性や保水性を

利用する用途分野に用いられるヒドロゲルとしては、水と接触して短時間の間にできるだけ多量の水を吸収する能力を有することが望まれる。

このようなヒドロゲルを製造する方法としてはポリエチレンオキシド、ポリアクリル酸、ポリビニルピロリドン、スルホン化ポリスチレン、ポリアクリル酸ソーダなどの水溶性高分子物質を架橋剤を用いて架橋する方法、親水基の一部を親油基で置換して水不溶性に変性する方法、アクリル酸アルカリ金属塩を重合し自己架橋させる方法等が提案されている。

しかし、上記方法に於いて重合を逆相懸濁重合法によつて実施した場合には、重合によつて生成したヒドロゲルを有機溶媒中より分離する際、ヒドロゲルが粘着し、塊状に凝固し、粒状形で得ることができない。その結果、機械的に粉砕しなければならないという操業上の繁雑化があり、加えて、生産性、収率の低下を招く等の欠点を有している。

このような欠点を改善する方法として、石油系脂肪族炭化水素溶媒中において、アクリル型アルカリ金属塩水溶液をH.L.B. 8～6のソルビタン脂肪酸エステル分散剤の存在下に重合させることにより、粉末化可能な自己架橋型アクリル酸アルカリ金属塩ポリマーの製造方法が提案されている（特開昭58－46889号公報）。

該特開昭の方法は、かなり有効な方法であるが充分満足されたものではなく、粉砕工程を無くするというレベルには達していない。

本発明者らは、上述の実情に鑑み、粒状又は球状でかつ十分なゲル強度を有する高吸水性のヒドロゲルを製造する方法に関して鋭意検討した結果、重合によつて生成したヒドロゲルを有機溶媒中より分離する際に、特定の化合物が存在する場合には、ヒドロゲル粒子同志の粘着を生ずることがなく、粒状のヒドロゲルを直接製造することが出来ることを見い出し、本発明を完成するに至つた。

すなわち、本発明はα，β－不飽和酸モノマーまたは／およびそのアルカリ金属塩を油中水滴型の逆相懸濁重合法によつて製造するヒドロゲルの製造法において、粘着防止剤としてヒドロゲルの乾燥温度以上の沸点及びヒドロゲルと溶媒の分離操作温度以下の融点を有する炭化水素油または／および油脂を用いることを特徴とする特別の粉砕処理を必要としないところの粒状又は球状ヒドロゲルの製造法を提供するにある。

本発明方法の実施に当り、粘着防止剤は重合によつて生成した粒状のヒドロゲルの分散乃至沈澱した有機溶媒から粒状のヒドロゲルを分離回収する際に生ずる、粒状のヒドロゲル同志の融着現象を実質的乃至完全に無くするものである。

かかる粘着防止剤の使用により重合によつて生成した粒状のヒドロゲルを融着を生ずることなく回収することが出来るという利点がある。それ故に、従来のように回収後、粉砕するという操作が不要となり極めて経済的である。

本発明方法の実施に当り用いられる粘着防止剤は、ヒドロゲルの回収系の乾燥温度以上の沸点、好ましくは乾燥温度より50℃以上高い沸点及びヒドロゲルと溶媒の分離操作温度以下の融点、好ましくは分離操作温度より20℃以上低い融点を有する炭化水素油または／および油脂であり、沸点が上記範囲を外れると、溶媒と分離したヒドロゲルを乾燥する段階で粘着防止剤が揮散し、得られるヒドロゲルが融着状態となるし、一方融点が上記範囲を外れると粘着剤が不均一に存在するとか、或いはヒドロゲルの表面を均一に被覆することができないために好ましくない。

好適には、沸点250℃以上及び融点30℃以下の炭化水素油または／および油脂が用いられる。

粘着防止剤としては流動パラフィン、綿実油、大豆油、ナタネ油、ヤシ油、液体ロウ、サラダ油、天ぷら油、ヘット、ラード等を挙げることができる。

特に、流動パラフィン、綿実油、大豆油等が好ましい。

粘着防止剤の適用方法は、重合系、すなわち重合前、重合途中に添加させてもよいし、また重合終了後の分散液又はスラリーに添加してもよい。

粘着防止剤の添加量は、一般にヒドロゲルに対して0.1重量%以上、好ましくは0.5～50重量%とされる。

添加量が0.1重量%未満になると粘着防止効果が僅かとなり、また多量に添加することは特に制限されるわけではないが経済的でないので一般に生成ヒドロゲルに対して100重量%位までである。

本発明方法は以下のようなヒドロゲルの製造法に適用される。

本発明方法において用いられるα，β－不飽和カルボン酸モノマーまたは／およびそのアルカリ金属塩モノマーとしてはアクリル酸、メタクリル酸、イタコン酸、クロトン酸、マレイン酸、フマール酸およびそれらのアンモニウム塩、アルカリ金属塩モノマー等を挙げることができる。

これらの中で特に好適に使用出来るものとしてはアクリル酸とメタクリル酸およびそれらのアルカリ金属塩モノマーを挙げることができる。

アルカリ金属としてはナトリウム、カリウム、カルシウム、バリウムなどを挙げることができる。

勿論、ヒドロゲルを製造する目的の範囲内で他のエチレン系不飽和単量体を共重合させることもできる。

重合媒体として用いられる有機溶媒としてはn－ヘキサン、n－ヘプタン、シクロヘキサン等の脂肪族炭化水素、ベンゼン、トルエン、キシレンなどの芳香族炭化水素等公知の有機溶媒を用いることができる。

本発明方法は逆相懸濁重合方法に於いて架かけ剤の存在下又は不存在下で重合を行なう系に適用できる。

架かけ剤を用いて製造したヒドロゲルは機械的強度が改善されるが、一般に吸水量は低下する。

これに対して架かけ剤を用いないで製造した自己架橋型のヒドロゲルは吸水量が高いという特徴を有している。

重合方法の選定はヒドロゲルの使用目的等により適宜なされる。

架かけ剤の存在下に重合を行う場合に用いられる架かけ剤としてはα，β－不飽和酸モノマーまたは／およびそのアルカリ金属塩モノマーと共重合可能なものであればよく、例えば、エチレングリコール、プロピレングリコール、トリメチロールプロパン、グリセリン、ポリオキシエチレングリコール、ポリオキシプロピレングリコール等のポリオール類のジ又はトリ（メタ）アクリル酸エステル類、前記ポリオール類とマレイン酸、フマール酸などの不飽和酸類とを反応させて得られる不飽和ポリエステル類、N，N－メチレンビスアクリルアミドなどのビスアクリルアミド類、ポリエポキシドと（メタ）アクリル酸とを反応させて得られるジまたはトリ（メタ）アクリル酸エステル類、トリレンジイソシアネート、ヘキサメチレンジイソシアネートなどのポリイソシアネートと（メタ）アクリル酸ヒドロキシエチルとを反応させて得られるジ（メタ）アクリル酸カルバミルエステル類、アリル化デンプン、アリル化セルローズ、ジアリルフタレート、N，N'，N''－トリアリルイソシアヌレート、ジビニルベンゼン等が挙げられる。

架かけ剤は一般に0.0001～1重量%、好ましくは0.001～0.5重量%の割合で使用するが、架かけ剤の割合が0.0001重量%より少なくなると生成ヒドロゲルの強度が低下し、一方、1重量%を超すようになるとヒドロゲルの吸水量が50%以下に低下するようになる。

重合に当り、α，β－不飽和カルボン酸モノマーおよび／またはそのアルカリ金属塩の有機溶媒中における濃度は一般に5～50重量%の

範囲内で、また、水／有機溶媒（重量比）は一般に0～50／100～50の範囲内で用いられる。

重合触媒の使用量はモノマーに対して一般に0.001～1重量%、好ましくは0.01～0.1重量%の範囲で用いられる。

重合触媒としては重合が逆相懸濁重合において水相で行なわれるために、過硫酸カリウム、過硫酸アンモニウム、過酸化水素又はこれらと亜硫酸水素ナトリウム、チオ硫酸ナトリウム、ピロ亜硫酸ナトリウム、ロンガリット等の適当な還元剤との併用系等の水溶性触媒が用いられる。

重合反応は一般に40～100℃で撹拌下に実施される。

重合の実施に当り使用される分散安定剤、界面活性剤としては、公知のものを使用することができる。好ましい分散安定剤、界面活性剤としては有機溶媒に対して親和性を有するカルボキシル基含有重合体、塩基性窒素含有重合体、および HLB が8～9の非イオン界面活性剤などをあげることができる。具体的にはカルボキシル基含有重合体としては、有機溶媒に対し親和性を有するカルボキシル基含有重合体であれば如何なるものでも用いることができるが、通常カルボキシル基を有する単量体とエチレン系不飽和単量体との共重合体、エチレン系不飽和単量体の単独又は共重合体に対してカルボキシル基を有する単量体を反応させた重合体、エチレン系不飽和単量体の単独又は共重合体に対してカルボキシル基を有する単量体をグラフト重合したグラフト共重合体、これらの変性物等が用いられる。

塩基性窒素含有重合体としては、有機溶媒に対し親和性を有する塩基性窒素含有重合体であれば如何なるものでも用いることができるが、通常塩基性窒素を有する単量体とエチレン系不飽和単量体との共重合体、エチレン系不飽和単量体の単独又は共重合体に対して塩基性窒素を有する単量体を反応させた重合体、エチレン系不飽和単量体の単独又は共重合体に対して塩基性窒素を有する単量体をグラフト重合したグラフト共重合体、これらの変性物等が用いられる。HLB が8～9の非イオン界面活性剤としてはソルビタンモノステアリン酸エステル、ソルビタンモノオレイン酸エステル、ソルビタンモノラウリル酸エステル、ソルビタンモノパルミチン酸エステル等のソルビタン脂肪酸エステル類、グリセリンモノステアリン酸エステル等のグリセリン脂肪酸エステル類、ショ糖ジステアリン酸エステル、ショ糖トリステアリン酸エステル等のショ糖脂肪酸エステル類およびこれらの混合物をあげることが出来る。使用されるこれらの分散剤、界面活性剤の量は仕込みモノマーに対して一般に0.01～20重量%である。重合反応生成物は沈降、戸過、遠心分離等の公知の手段によりヒドロゲルと有機溶媒とを分離する。分離操作は一般に10～100℃の温度で実施される。

分離されたヒドロゲルは次いで静置乾燥機、棚式減圧乾燥機、撹拌機つき減圧乾燥機、ロータリー式乾燥機、流動乾燥機、気流型乾燥機等の公知の手段により乾燥される。乾燥温度は重合に用いる有機溶媒の種類等により異なるが、一般に20～150℃の温度で実施される。かくして、重合系又は重合後に粘着防止剤を添加した本発明方法によれば、乾燥して得られたヒドロゲルが粘着したり塊状に凝固することがなく、機械的粉砕などの工程を必要としないで粒状のヒドロゲルを製造することができる。

以上詳述した本発明方法によつて製造されたヒドロゲルは分散剤、界面活性剤の種類、添加量等によつても変わるが一般に平均粒子径が約20～8000μの範囲で任意にコントロールされたヒドロゲルを粉砕処理を必要とせずして製造することが可能である。

本発明方法によつて製造された粒状のヒドロゲルは十分なゲル強度及び優れた吸水能力を有している。

以下に実施例を挙げて本発明方法を更に詳細

に説明するが、本発明はこれらに限定されるものではない。なお、実施例中ヒドロゲルの吸水率は

吸水率＝（吸水ヒドロゲル重量）／（乾燥ヒドロゲル重量）(818)

で表示した。また、部数は重量単位である。

平均粒径は篩別法によつて求めた。さらにゲルの強度は飽和吸水ゲル粒子の圧壊強度を

ゲル強度＝（圧壊荷重）／π（飽和吸水ゲル半径）

により表示した。

実施例1

5ℓのフラスコにメタクリル酸とメタクリル酸ブチルをグラフトしたエチレン－プロピレン－ジエンモノマー共重合体（以下EPDMと略記する。カルボキシル基含量＝6.6モル%）140g、第1表に示す種類および量の粘着防止剤をn－ヘキサン2ℓに溶解させて添加した。一方、水270ml、アクリル酸200gと水酸化ナトリウム90gを混合した後、過硫酸カリウム150mgとN，N'－メチレンービス－（アクリルアミド）を80mg加え、アクリル酸ナトリウム水溶液を調整した。このアクリル酸ナトリウム水溶液を上記5ℓフラスコ内に200rpmで撹拌しながら滴下し、60℃で8時間重合させた。重合後、重合反応生成物を室温で遠心沪過分離してヒドロゲルを分離した。得られたヒドロゲルを棚型乾燥機で80℃で10時間乾燥させた。得られたヒドロゲルの粒子状態を第1表に示した。実験番号1－1および1－5（比較例）のヒドロゲルの粒子状態を示すと第1図および第2図に示す通りである。本法によると各粒子が凝集することなく得られる。得られたヒドロゲルの特性を例示すると、実験番号1－1においては、平均粒径は700μで吸水率は600g/gでありゲル強度は800g/cmであつた。

第1表

実験番号	粘着防止剤 物質名	粘着防止剤 融点(℃)	粘着防止剤 沸点(℃)	粘着防止剤 添加量(重量%)*	ヒドロゲル粒子の状態 分離工程	ヒドロゲル粒子の状態 乾燥工程
1－1	流動パラフィン	−80℃以下	250℃以上	10	粘着・凝集を認めず	凝集粒を認めず
1－2	〃	〃	〃	1	〃	〃
1－3	綿実油	〃	〃	20	〃	〃
1－4	大豆油	〃	〃	20	〃	〃
1－5（比較例）	—	—	—	0	粘着・凝集した	塊状になり粉砕を必要とした
1－6（〃）	流動パラフィン	−80℃以下	250℃以上	0.05	一部粘着・凝集した	約60%凝集粒が発生した
1－7（〃）	固体ロウ	80℃以上	800℃以上	5	粘着・凝集した	塊状になり粉砕を必要とした

*）ヒドロゲルに対する添加（以下同じ）

実施例2

10ℓフラスコに無水マレイン酸変性液状ポリブタジエンのメタクリル酸2－ヒドロキシエチルとの半エステル化合物（カルボキシル基含量＝5.2モル%）15gをトルエン4.5ℓに溶解させて添加した。

一方、水600ml、アクリル酸450g及び水酸化ナトリウム201gを混合した後、過硫酸カリウム1.35gを加えアクリル酸ナトリウム水溶液を別途調整した。このアクリル酸ナトリウム水溶液を上記10ℓフラスコ内に250rpmで撹拌しながら滴下し、70℃で8時間重合させた。重合後、第2表に示す種類及び量の粘着防止剤を添加し70℃で80分間撹拌した。

重合後、重合反応生成物を80℃で遠心沪過分離してヒドロゲルを分離した。分離したヒドロゲルを撹拌機付き減圧乾燥機で80℃で10時間減圧乾燥させた。得られたヒドロゲルの粒子状態を第2表に示した。

得られたヒドロゲルの特性は実験番号2－1において、平均粒径170μ、吸水率1500g/gであり、ゲル強度は500g/cmであつた。

第2表

	粘着防止剤					ヒドロゲル粒子の状態	
	実験番号	物質名	沸点	融点	添加量(重量%)	分離工程	乾燥工程
	2－1	流動パラフィン	250℃以上	−30℃以下	0.5	粘着・凝集を認めず	〃
	2－2	〃	〃	28～25℃	10	〃	〃
	2－3	ヤシ油	200℃以上	23℃	6	〃	〃
	2－4	液体ロウ	〃	−10℃以下	10	〃	〃
	2－5(比較例)	—	—	—	—	粘着・凝集した	塊状になり粉砕を必要とした
	2－6(比較例)	固体ロウ	300℃以上	82－84℃	5	粘着・凝集した	塊状になり粉砕を必要とした

実施例8

10ℓのフラスコに第8表に示した分散剤／界面活性剤280g、第8表に示す種類及び量の粘着防止剤をnヘキサン4ℓに溶解させて添加した。一方、水540ml、アクリル酸400gと水酸化ナトリウム180gを混合した後、過硫酸カリウム300mgとN，N'－メチレンービスー（アクリルアミド）を60mg加え、アクリル酸ナトリウム水溶液を調整した。このアクリル酸ナトリウム水溶液を上記10ℓフラスコに200 rpmで攪拌しながら滴下し、60℃で3時間重合させた。

重合後、重合反応生成物を室温で第8表に示す分離機を用いてヒドロゲルを分離した。得られたヒドロゲルを第8表に示す乾燥機を用い80℃で10時間乾燥させた。

得られたヒドロゲルの粒子状態を第8表に示した。得られたヒドロゲルの特性は実験番号8－1において、平均粒径45μ、吸水率400g/gであり、ゲル強度は250g/cmであつた。

また、実験番号8－2の方法において、粘着防止剤を重合時に添加しないで、重合途中において添加した以外は全く同様にして重合し、後処理した。

その結果実験番号8－2と同様の結果が得られた。

以上の結果より、本発明方法は極めて有用な方法であることが理解できる。

第 8 表

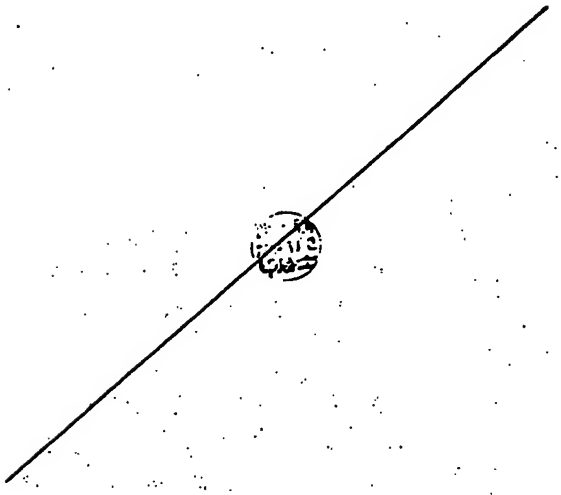
実施番号	分散剤／界面活性剤	沸点防止剤 物質名	沸点(℃)	融点(℃)	添加量(重量%)	熱処理工場 分離工程	熱処理工場 乾燥工程	ヒドロゲル粒子の状態
8-1	ソルビタンモノステアレート	流動パラフィン	250℃以上	−8℃以下	7	吸引戸過	棚式減圧乾燥機	凝集粒を認めず
8-2	エチレン−アクリル酸共重合体（アクリル酸含有率20重量%）	〃	〃	〃	7	遠心戸過	流動乾燥機	〃
8-3	メタクリル酸−2−ヒドロキシエチル−N,N−ジメチルアミノエチルアクリレート共重合体（重量組成比 95:5）	〃	〃	〃	10	遠心戸過	ロータリー式減圧乾燥機	〃
8-4	ソルビタンモノステアレート	—	—	—	—	吸引戸過	棚式減圧乾燥機	塊状になり粉砕を必要とした

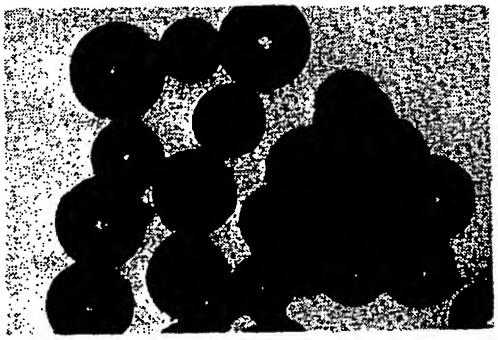
4. 図面の簡単な説明

第１図は本発明方法で製造されたヒドロゲルの顕微鏡写真である。

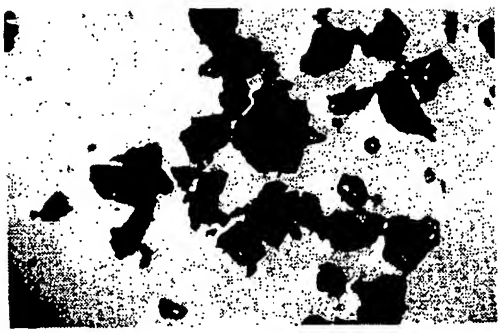
第２図は公知方法で製造されたヒドロゲルを電動ミキサー（８０００ rpm ）で粉砕したものの顕微鏡写真である。

いずれも倍率５０倍である。





第１図



第２図

手 続 補 正 書（自発）

昭和56年 4 月 27 日

特許庁長官 島 田 春 樹 殿

1. 事件の表示

昭和56年 特許願第 15289号

2. 発明の名称

ヒドロゲルの製造法

3. 補正をする者

事件との関係 特許出願人

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5. 補正の対象

明細書の「発明の詳細な説明」の欄

6. 補正の内容

明細書を次のとおり補正する。

(1) 明細書第4頁第1行の「アクリル型」を「アクリル酸」に訂正する。

(2) 明細書第4頁最下行の「不飽和酸」を「不飽和カルボン酸」に訂正する。

(3) 明細書第15頁第5行の「818」を「9/9」に訂正する。

(4) 明細書第15頁第6行の「また、部数は重量単位である」を削除する。

(5) 明細書第15頁第9行の「R_{π}（飽和吸水ゲル半径）」を「R_{π}（飽和吸水ゲル半径）'」に訂正する。

(6) 明細書第15頁第16行の「140g」を「149」に訂正する。

(7) 明細書第21頁第8行の「2809」を「289」に訂正する。

(8) 明細書第28頁第8表の実験番号の欄「8－4」の下に「（比較例）」を加入する。

以 上

(H3)

SUSPENSION FOR BLOOD VESSEL EMBOLIZATION

Patent number:	JP6056676
Publication date:	1994-03-01
Inventor:	HORI TOMOKO
Applicant:	SHINICHI HORI
Classification:	
- international:	A61K31/78; A61K9/107
- european:	
Application number:	JP19920250360 19920805
Priority number(s):	

Abstract of **JP6056676**

PURPOSE:To provide a suspension to be injected through a catheter into the blood vessel for occluding specific parts.

CONSTITUTION:This suspension for blood vessel embolization is prepared by suspending a high water-absorbing resin particles which are mainly made of a polymer from sodium acrylate or a copolymer from sodium acrylate and vinyl alcohol and have an average particle size of less than about 1.0mm diameter in an oily contrast medium.

Family list
1 family member for:
JP6056676
Derived from 1 application.

1 SUSPENSION FOR BLOOD VESSEL EMBOLIZATION
Publication info: JP6056676 A - 1994-03-01

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(19)日本国特許庁（ＪＰ）　(12)公開特許公報（A）　(11)特許出願公開番号

特開平6－56676

(43)公開日　平成6年(1994)3月1日

(51)Int.Cl.[5]	識別記号	庁内整理番号	FI	技術表示箇所
A61K 31/78	ABN	8314-4C		
9/107		Z 7329-4C		

審査請求　未請求　請求項の数1(全 8 頁)

(21)出願番号　特願平4－250360

(22)出願日　平成4年(1992)8月5日

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(54)【発明の名称】　血管塞栓用懸濁液

(57)【要約】　(修正有)

【目的】　血管の特定部分を塞栓するために、カテーテルを介して注入される血管塞栓用懸濁液を提供する。

【構成】　アクリル酸ソーダの重合体又はアクリルソーダとビニルアルコールとの重合体を主成分とし、平均粒子径を約1．0mm以下とする高吸水性樹脂粒子を油性造影剤に懸濁させてなる血管塞栓用懸濁液。

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【特許請求の範囲】

【請求項1】　アクリル酸ソーダの重合体又はアクリルソーダとビニルアルコールとの重合体を主成分とし、平均粒子径を約1．0mm以下とする高吸水性樹脂粒子を油性造影剤に懸濁させてなる血管塞栓用懸濁液。

【発明の詳細な説明】

【0001】

【産業上の利用分野】この発明は血管塞栓用懸濁液に関し、更に詳しくは、血管の特定部分を塞栓するために、カテーテルを介して注入される血管塞栓用懸濁液に関する。

【0002】

【従来の技術及び発明が解決しようとする課題】従来、動脈塞栓術、特に頭蓋内の動静脈奇形の塞栓術に用いられているCyanoacrylates（シアノアクリレート）（isobutyl－2－cyanoacrylate，n－butyl cyanoacrylate）は、有用な塞栓物質として認められているが、nidus（動静脈奇形の短絡部分）で重合させる為に濃度などの調整を行うのに経験を要すること、しばしばカテーテル内で重合しカテーテルの閉塞を起こしたり、カテーテルと重合したCyancacrylatesとが接着を起こす危険があるなどの欠点を有する。接着性の問題を解決するために少量のCyanoacrylatesを数回に分けて注入する方法も提案されているが、細心の注意が必要であることに変わりはない。これらのcyanoacrylatesの欠点を補うためにEVAL（Ethylene Vinyl Alcohol Copolymer）が多くの施設で用いられているが、有機溶媒を必要とし、カテーテルとの適合性が悪い場合があり、扱い易く毒性のない塞栓物質の開発が望まれている。一方、塞栓材料にPolyvinyl Alcohol（PVA）や縫合糸を用いる報告も多いが、カテーテルをしばしば閉塞し、更に動脈が中枢側で塞栓されるため動静脈奇形の再開通の率が高く、なるべくnidusに近い場所で塞栓できる材料が望ましい。このためEthanolやAvitene（microfibrillarcollaten）を混ぜて使うなどの工夫が必要である。かくして頭蓋内の塞栓術に際して塞栓物質に求められる条件は、極めて細かいカテーテルを通過すること、造影性がよいこと、nidusを通過しないこと、永久塞栓効果をもつこと、毒性のないことが挙げられる。

【0003】

【課題を解決するための手段及び作用】この発明はアクリル酸ソーダの重合体又はアクリルソーダとビニルアルコールとの重合体を主成分とし、平均粒子径を約1．0mm以下とする高吸水性樹脂粒子を油性造影剤に懸濁させてなる血管塞栓用懸濁液である。すなわちこの発明は、高吸水性樹脂粒子が水分、つまり血液（中の水分）

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と出会うことにより瞬時に吸水膨潤する（例えば自重の1000倍の水分を吸収し膨潤する）ことを利用して血管を塞栓物質として作用させようとするものであり、更にその高吸水性樹脂粒子を油性造影剤に懸濁させることによって、上記吸水膨潤を遅らせ、塞栓物質としての作用がカテーテル内部やカテーテル隣接個所ではなく、血管の所望の個所のみで起こるようにするものである。

【0004】この発明において使用される高吸水性樹脂粒子は主成分をアクリル酸ソーダの重合体、又はアクリル酸ソーダとビニルアルコールとの重合体とする。特にこれらの主成分として酢ビーアクリル酸エステル共重合体ケン化物、酢ビーマレイン酸メチル共重合体けん化物、イソ・ブチレンー無水マレイン酸共重合体架橋物、でん粉ーアクリルニトリルグラフト共重合体ケン化物、架橋ポリアクリル酸ソーダ、ポリエチレンオキサイドの架橋物などが具体例として挙げられる。

【0005】これらの高吸水性樹脂粒子は、平均粒子径を約1．0mm以下とし、好ましくは0．9mm以下とするものが使用される。更にこれらの平均粒子径を適宜選択することによって、血管の所望個所を塞栓できる。

【0006】この発明においては、これらの高吸水性樹脂粒子を油性造影剤に懸濁させ懸濁液とされる。この場合油性造影剤1mlに対して高吸水性樹脂粒子10～20mgを懸濁させるのが好ましい。この油性造影剤としては、ヨード化ケン油脂肪酸エチルエステルからなる造影剤〔リピオドール（登録商標）〕、アミドトリゾ酸（無水物として）、水酸化ナトリウム及びメグルミンを含有する造影剤〔ウログラフィン（登録商標）〕、アミドトリゾ酸（無水物として）及びメグルミンを含有する造影剤〔アンギオグラフィン（登録商標）〕などが挙げられる。得られた懸濁液は、カテーテルによって血管の特定個所（例えば動脈）に注入されると、高吸水性樹脂粒子が油性造影剤に包まれた状態で血管の末梢まで流れ、そこで被膜の油分が離れ血液中の水分と出会うと瞬時に（例えば2－3秒）水分を吸収し、直径を増して（例えば4．5倍）塞栓物質として作用する。

【0007】以下この発明に係る血管塞栓用懸濁液の使用例を挙げる。

【0008】イ）悪性腫瘍の塞栓例

血管が乏しいもの　N－100（S）とリピオドールの懸濁液（10mg／ml）

血管が豊富なもの　N－100（M）あるいはN－100（L）とリピオドールの懸濁液（10mg／ml）

N－100とS－50を混ぜ、リピオドールとの懸濁液を作る（10～15mg／ml）、但しN－100：アクリル酸ソーダ重合体、S－50：アクリル酸・ビニルアルコール共重合体、（S）（M）（L）は粒子の大きさを示し、順に平均粒径で0．20mmφ、0．53mmφ、0．88mmφである。

【0009】ロ）動静脈瘤（AVM）の塞栓例

Low Flow Type：N－100（S）とピオドールの懸濁液（10mg／ml）

High Flow Type：N－100とS－50を混ぜ、リピオドールとの懸濁液を作る（10～15mg／ml）

【0010】ハ）動脈出血の塞栓例

出血している血管の径より少し大きい径のS－50を数個づつ数えて造影剤と懸濁させ、その懸濁液を出血が止まるまで注入する。

【0011】

【実施例】

実施例1

この発明に係る血管塞栓用懸濁液が実際に塞栓効果を持つことを確かめるため動静脈瘤を想定した図1のごとき塞栓血管モデル（1）を作製した。塞栓血管モデル（1）は、約2．0mlの容積を持つプラスチックチャンバー（2）のなかに円筒形（高さ2mm、直径18mm）のウレタンフォームスポンジ（連続気泡体）（3）を充填したものである。血液はこのチャンバー（2）を抵抗なく通過する。この塞栓血管モデル（1）500ml1から1，000mlの生理的食塩水のボトル（4）を接続し、このボトルに自動加圧装置（5）を用いて150mmHgの定常圧を加え、定常流をチャンバー（2）に流した。なお（6）は圧力計、（7）はマイクロカテーテルである。ウレタンフォームスポンジとして次の2種類をのものを充填した。つまり

low flow type：ウレタンフォームの目の大きさ平均0．5mm

high flow type：ウレタンフォームの目の大きさ平均0．9mm

生理的食塩水の流速を測定して塞栓効果を判定した。

【0012】イ）low flow type AVM modelの塞栓（図1、図2、図4参照）

N－100（S）の76％ウログラフィンとリピオドール混合液の懸濁液を用いると、N－100（S）40mgて水流停止する。一方、N－100（M）を用いると、同様の懸濁液で、5mg以下で水流停止する。N－100の量が多いほど、またその粒子径が大きいほど、詰まり易い。

【0013】ロ）high flow type AVM modelの塞栓（図1、図2、図5参照）

N－100（M）の76％ウログラフィンとリピオドール混合液の懸濁液では、塞栓効果は認められない。S－50（M）を加えることにより、塞栓効果が現れる。N－100（L）＋S－50（L）では、10mgの少量で塞栓効果か現れる。N－100（S）＋S－50（S）では、塞栓効果はない。N－100（S）＋S－50（S）でも、アンギオグラフィンで懸濁させるとS－50の粒子がおおきくなり、塞栓効果をもつようになる。これらにより、血流の速いAVMの塞栓にはS－50を混合することが極めて大事である。

【0014】臨床例

イ）26歳の女性　中絶後子宮出血

骨盤動脈撮影：右子宮動脈の拡張と、子宮に一致して螺旋状に拡張した異常血管が認められる。また、血管外へ造影剤の漏出が認められ、出血が確認できた。

選択的右子宮動脈：カテーテルを右子宮動脈に選択的に挿入して、造影を行っている。

選択的右子宮動脈造影（塞栓術後）：S－50（M）5mgを整理食塩水で吸水させてからリピオドールに懸濁させカテーテルより注入した後、撮影を行った。異常血管は消失し血管外へ造影剤の漏出も認められなくなり、正常の子宮動脈筋肉のみが描出されている。術後、子宮からの出血は停止した。

以上この発明に係る血管塞栓用懸濁液を使用した場合の塞栓物質としての特徴を列挙すれば次のとおりである。

イ）毒性・刺激性がない：この点については、既にデータがある。従来の塞栓物質の組織反応の研究から想像する限りでは、特に問題とはならない。10例の臨床経験で、注入時の痛みはまったくない。

ロ）粘調度が低い：リピオドールの粘調度より少し高い程度で極めて高濃度の懸濁液でなければ1．0mlの注射器でマイクロカテーテルに通すことができる。

ハ）造影性がよい：懸濁液としてリピオドールを使っているので透視下で極めてよく見える。また、塞栓部位にリピオドールが貯溜することで塞栓効果が確かめられる。

ニ）カテーテルを閉塞しない：粒子が凝集する性質がないので、カテーテルを詰まらせない。接着性がないためにカテーテルと血管が接着される危険がない。

ホ）塞栓部位を調節できる：粒子の大きさを調節できる。その方法は、（S）（M）（L）で調節するか、懸濁させる造影剤により粒子の大きさを調節する。このことにより、あらかじめ塞栓できる血管径を決めることが出来る。

【0015】

【発明の効果】この発明に係る血管塞栓用懸濁液を用いれば、毒性・刺激性がなく、粘調度が低く、造影性が良好で、カテーテルを閉塞せず、しかも塞栓部位を調節できるという効果が得られる。

【図面の簡単な説明】

【図1】N－100（10mg）が吸収できる液体の量を示す説明図である。

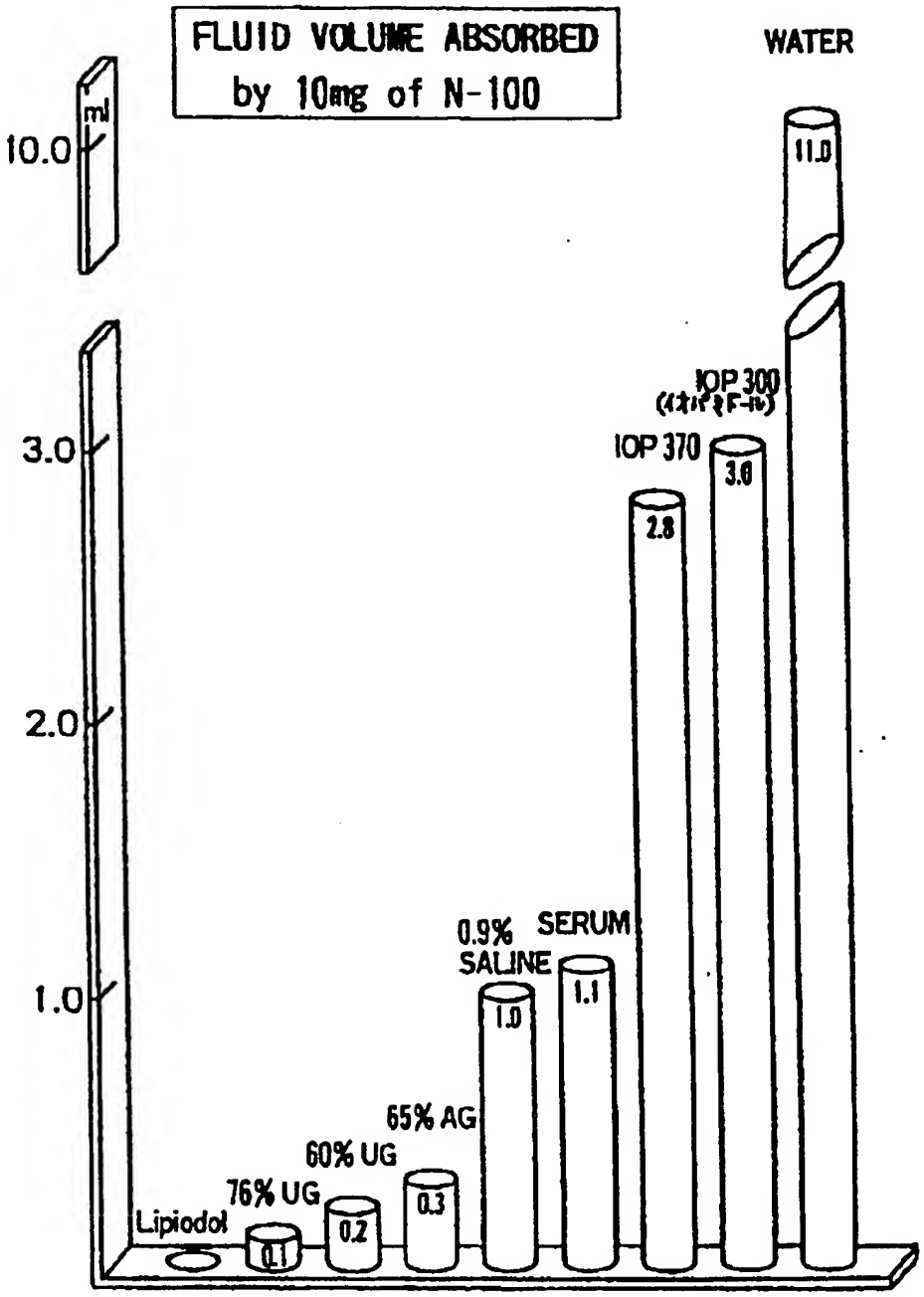
【図2】種々の液体の存在下でのS－50の直径の変化を示す説明図である。

【図3】塞栓血管モデルの概略構成説明図である。

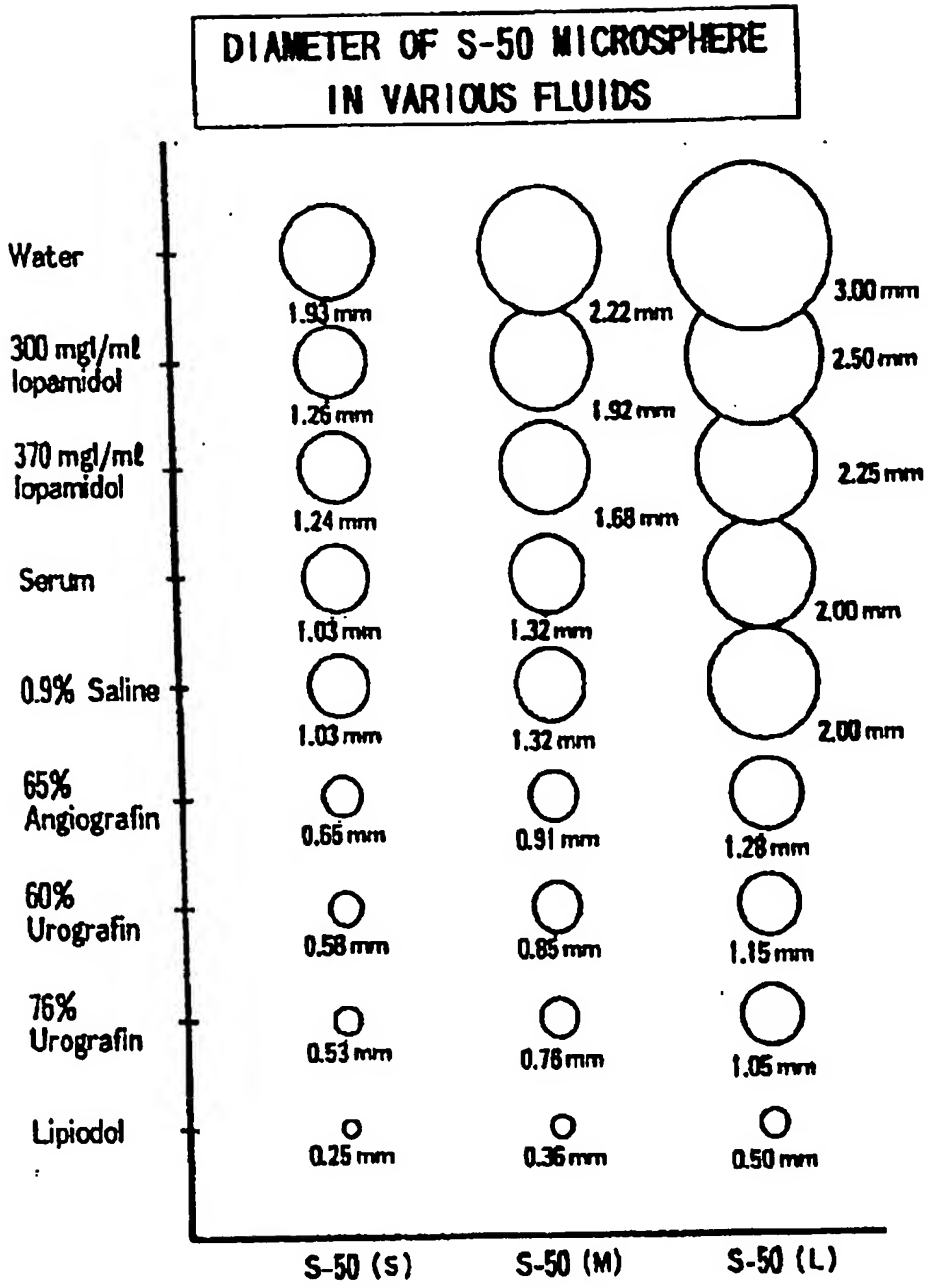
【図4】LOW FLOWモデルの塞栓効果を示すグラフである。

【図5】HIGH FLOWモデルの塞栓効果を示すグラフである。

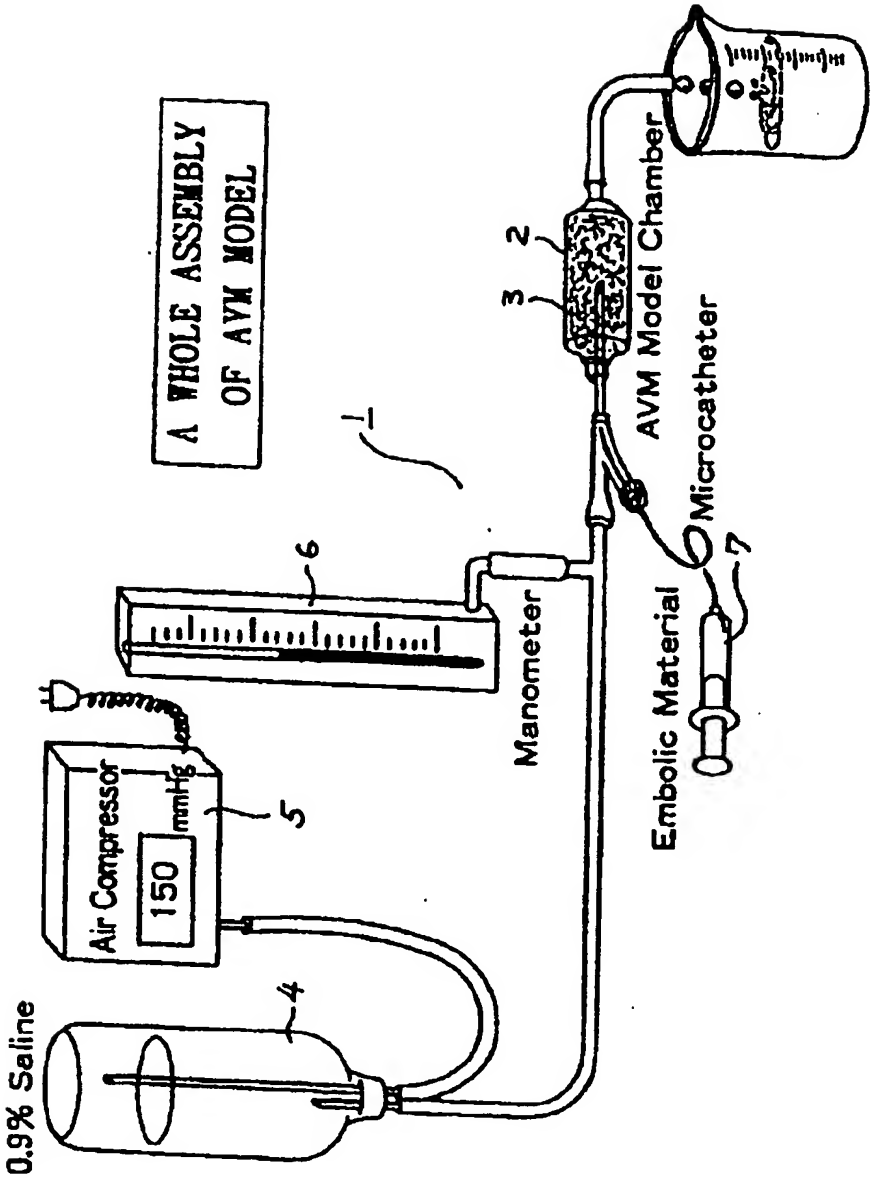
【図1】


FLUID VOLUME ABSORBED
by 10mg of N-100
ml
10.0
3.0
2.0
1.0
WATER
11.0
IOP 300
IOP 370
3.8
2.8
0.9% SERUM
SALINE
1.1
1.0
65% AG
0.3
60% UG
0.2
76% UG
0.1
Lipiodol

【図2】

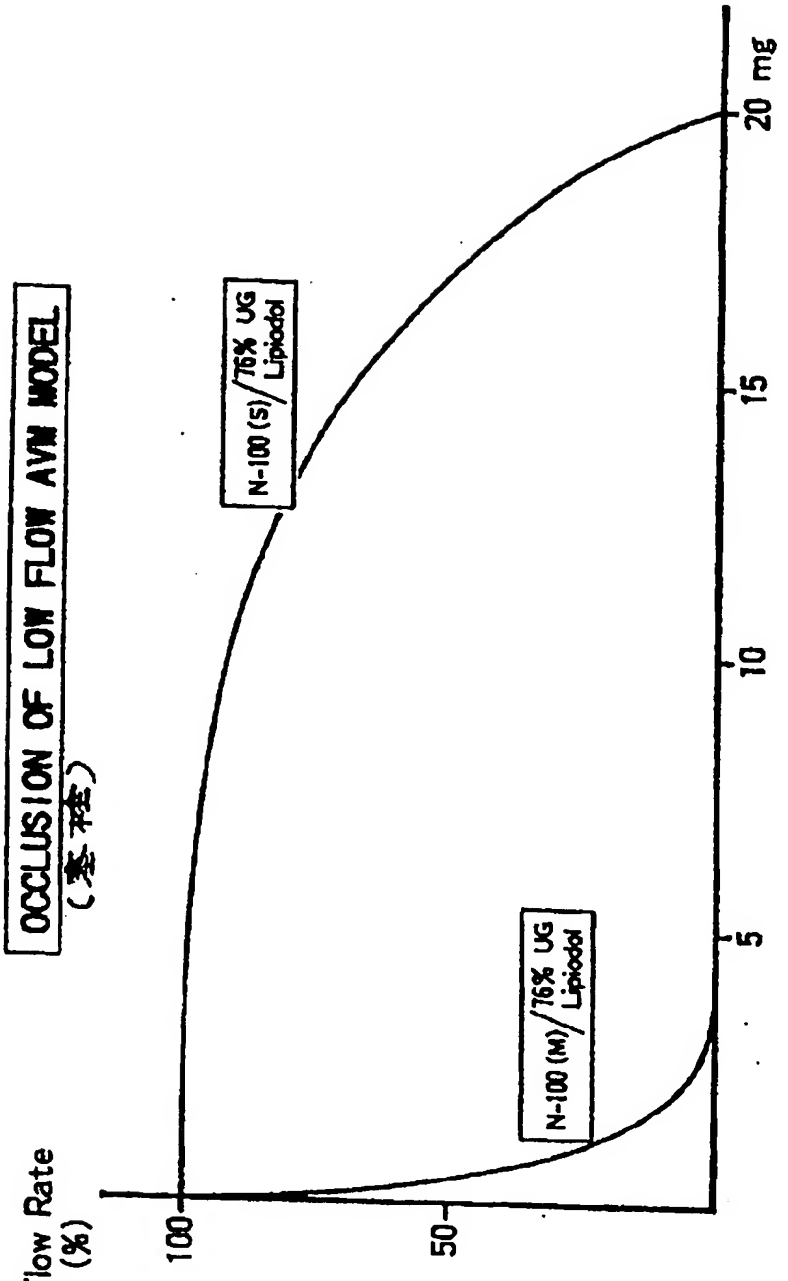

DIAMETER OF S-50 MICROSPHERE IN VARIOUS FLUIDS
Water
300 mgI/ml Iopamidol
370 mgI/ml Iopamidol
Serum
0.9% Saline
65% Angiografin
60% Urografin
76% Urografin
Lipiodol
1.93 mm
2.22 mm
3.00 mm
1.26 mm
1.92 mm
2.50 mm
1.24 mm
1.68 mm
2.25 mm
1.03 mm
1.32 mm
2.00 mm
1.03 mm
1.32 mm
2.00 mm
0.65 mm
0.91 mm
1.28 mm
0.58 mm
0.85 mm
1.15 mm
0.53 mm
0.76 mm
1.05 mm
0.25 mm
0.36 mm
0.50 mm
S-50 (S)
S-50 (M)
S-50 (L)

【図3】


A WHOLE ASSEMBLY
OF AVM MODEL
1
2
3
AVM Model Chamber
Microcatheter
7
Embolic Material
Manometer
6
5
Air Compressor
150
mmHg
4
0.9% Saline

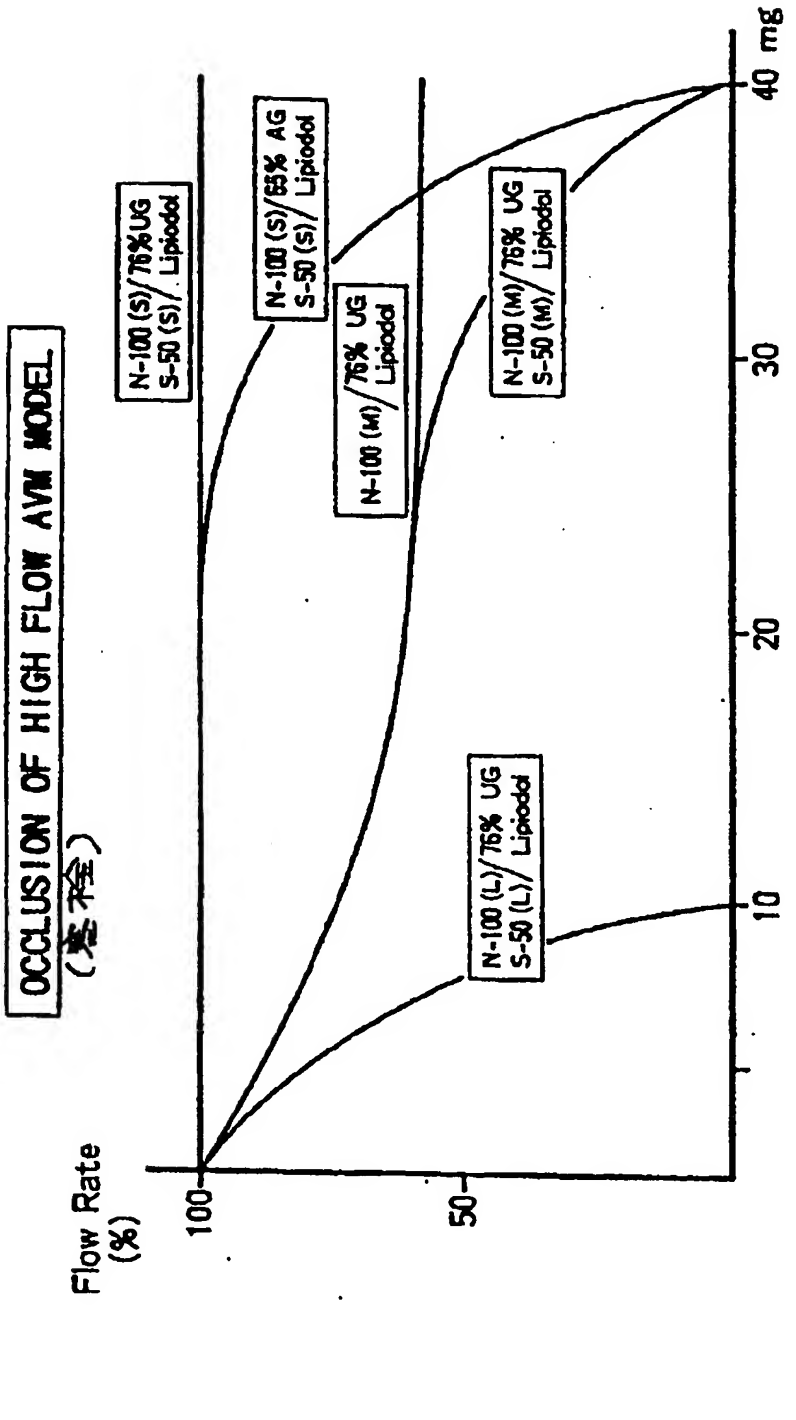
【図3】

【図4】


OCCLUSION OF LOW FLOW AVM MODEL
(豚腎)
Flow Rate
(%)
100
50
5
10
15
20 mg
N-100 (S)/76% UG Lipiodol
N-100 (M)/76% UG Lipiodol

【図十】

【図5】


OCCLUSION OF HIGH FLOW AVM MODEL
(高粘性)
Flow Rate (%)
100
50
10
20
30
40 mg
N-100 (S)/76%UG S-50 (S)/ Lipiodol
N-100 (S)/65% AG S-50 (S)/ Lipiodol
N-100 (M)/76% UG Lipiodol
N-100 (M)/76% UG S-50 (M)/ Lipiodol
N-100 (L)/76% UG S-50 (L)/ Lipiodol

【図5】

I1

P-072

Transcatheter embolization of iatrogenic vascular lesions of celiac trunk branches

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Purpose : To describe the role of angiographic evaluation and selective transcatheter embolization of iatrogenic lesion of celiak trunk branches.

Materials and Methods : We treated five cases of upper gastrointestinal bleeding due to injuries of the celiac trunk branches: four arterial ruptures (two hepatic arteries, one gastroduodenal, one pancreatic-duodenal) and a false aneurysm of the gastroduodenal artery. The iatrogenic causes of bleeding were hepatic biopsy (one case), biliary percutaneous transhepatic drainage (one case), endoscopic sphincterotomy (two cases) and surgical antrectomy (one case). All the vascular lesions were disclosed by abdominal selective angiography. In all cases, the feeding vessel was then catheterized by microcatheter and embolized by microcoil (0.018").

Results : An immediate technical success was obtained. No complication related to the procedure occurred. Transcatheter embolization of the lesions allowed for a full recovery of the patients confirmed by subsequent follow-up.

Conclusion : Splanchnic vessels lesions are a quite rare complication of surgical, endoscopic and percutaneous procedures, often presenting a life-threatening problem. In such emergency cases, the selective abdominal arteriography represents the elective diagnostic tool, able to disclose the site and, frequently, the cause of bleeding. Furthermore, angiography may be followed by transcatheter embolization, thus effectively controlling the hemorrhage and obviating the need for a difficult surgical intervention.

P-073

Angiographic diagnosis and percutaneous management of lumbar artery injuries

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Purpose : To evaluate angiographic findings and embolotherapy in the management of lumbar artery injuries.

Materials and Methods : We retrospectively reviewed all the cases with lumbar artery injury who have undergone angiography and percutaneous embolization within a ten-year period. Radiologic information and procedural reports were reviewed to assess immediate angiographic findings and embolization results. Long-term clinical outcome was obtained by communication with the trauma physicians as well as with chart review.

Results : Over the last ten-year period, 255 trauma patients have undergone abdominal aortography. In ten of these patients (three women and seven men) a lumbar arterial injury was demostrated. Eight patients were found to have active extravasation and two had pseudoaneurysms. Successful selective embolization of an abnormal vessel(s) was performed in all patients. Coils were used in two patients, particles in one, and gelfoam in seven patients. Complications included one retroperitoneal abscess and one patient needed to return for embolization of a different lumbar artery due to pseudoaneurysm formation.

Conclusion : In hemodynamically stable patients, selective embolization is an effective and safe method to control active extravasation, as well as to prevent future hemorrhage and delayed complications of lumbar arterial injuries.

P-074

Transcatheter embolization as the definitive treatment for hepatic traumas

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Purpose : Massive hemorrhage is a severe complication of liver trauma. Surgery is frequently contra-indicated due to comorbidities. We present our experience with the percutaneous embolization of hepatic traumas.

Materials and Methods : Eighteen patients (12 men), with liver injury were treated by embolization. The bleeding was related to pseudoaneurysms of the hepatic artery (HA) in all cases (MVA in 11, surgery in four, needle biopsy in two and percutaneous biliary drainage in one). Hemobilia was present in seven patients, laceration with bleeding in five, and hypotension in six.

Results : The lesion was in the right (n=15), left (n=1), proper (n=1) and both left and right (n=1) HA. Embolization used a combination of coils and Gelfoam pledgets (n=10), Gelfoam alone (n=3), coils alone (n=2), blood clot (n=1), n-butyl-cyanoacrilate (n=1) and occluding balloon catheter (n=1). Treatment by embolization was successful in 17 patients. There were two deaths, one due to uncontrolled bleeding despite embolization an one due to multiple organ failure.

Conclusion : Transcatheter embolic therapy is effective for the treatment of hepatic traumas. High-risk patients can be treated without surgery. It is our impression that transcatheter embolization should be considered in the first line of treatment for acute and severe traumatic hepatic bleeding.

P-075

Embolotherapy of large hepatocellular carcinomas (HCC) using a new permanent, spherical embolic material without anti-neoplastic agents

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Purpose : To improve the therapeutic effects on large HCCs and the patients' quality of life by embolotherapy using a permanent, spherical embolic material without antineoplastic agents.

Materials and Methods : Superabsorbent poloymer microspheres (SAP-MS) are spherical, non-absorbable particles that expand twice their original size when mixed with Hexabrix 320. In the occlusion point, they further expand by absorbing the serum without toxicity or tissue irritability. The size of the microspheres ranged from 0.050 to 0.100 mm. A total of 14 patients with large HCCs (mean diameter: 9.5 cm) was treated by embolization with SAP-MS without anti-neoplastic agents or Lipiodol. A microcatheter was used in all cases. Embolization was terminated when the tumor vascularity or the feeding arteries disappeared.

Results : There were no complications during and after the procedure, except for a slight pain and fever which were well controlled by oral antipyretics. The patients' quality of life was always better than with conventional chemoembolization. Tumor volume reduction rate went from 40 to 70% in three months. One- and two-year survival rates were 58 and 52%, respectively.

Conclusion : The therapeutic effects of this procedure for larger HCC and survival rates were acceptable. A good post-treatment quality of life is of great advantage over conventional chemoembolization.

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CardioVascular & Interventional Radiology

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I2

ORIGINAL ARTICLE

Radiation Medicine: Vol. 22 No. 6, 384–390 p.p., 2004

Embolic Effects of Superabsorbent Polymer Microspheres in Rabbit Renal Model: Comparison with Tris-acryl Gelatin Microspheres and Polyvinyl Alcohol

Azzam A. Khankan,* Keigo Osuga,* Shinichi Hori,* Eiichi Morii,** Takamichi Murakami,* and Hironobu Nakamura***

Purpose: We have developed a spherical embolic agent, superabsorbent polymer microspheres (SAP-MS). The aim of this study was to examine the embolic effects of SAP-MS in comparison with polyvinyl alcohol (PVA) particles and tris-acryl gelatin microsphere (Embosphere Microsphere; EM) in a rabbit renal model.

Materials and Methods: The right kidneys of nine rabbits were embolized with the given agents: PVA (180-300 μm) (n=3), EM (100-300 μm) (n=3), and SAP-MS (106-150 μm) (n=3). The embolized kidneys were evaluated by angiography and histology after one week.

Results: Renal artery occlusion and prominent coagulative necrosis were confirmed regardless of agent. PVA aggregated in the proximal vessels with tiny fragments migrating into glomeruli. Both EM and SAP-MS traveled distally up to the interlobular artery level, and a single particle achieved cross-sectional vessel occlusion. SAP-MS was markedly swollen, deformed, and conformed to the vessel lumen compared with the constantly spherical EM. Mild perivascular reaction was seen with both microspheres.

Conclusion: SAP-MS resulted in targeted end-organ infarction in the rabbit renal model and showed different mechanical properties from other agents.

Key words: superabsorbent polymer microsphere, Embosphere Microsphere, polyvinyl alcohol particles

Introduction

Polyvinyl alcohol (PVA) has been the standard particulate embolic agent for transcatheter embolization (TAE), and it has been proved to be both useful and biologically inert. However, unpredictable proximal vessel occlusion and microcatheter blockage caused by clumping of irregular-shaped PVA particles have been described.[1,2] Recently, the interest in spherical agents has grown, to overcome the drawbacks of PVA, and different microspheres have been developed.[1,3-7] Tris-acryl gelatin microspheres have become the most popular in clinical use especially for uterine fibroid embolization.[8] Because neither tris-acryl gelatin microspheres nor standard PVA particles have been approved in Japan, we developed a spherical agent, superabsorbent polymer microspheres (SAP-MS), and applied it clinically in cases of hypervascular tumors and peripheral arteriovenous malformations.[5-7]

The purpose of this study was to describe the radiologic and histologic characteristics of SAP-MS by comparing them with tris-acryl gelatin microspheres and PVA particles in a rabbit renal model.

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Materials and Methods

Embolic agents

SAP-MS (sodium acrylate and vinyl alcohol copolymer) was compared with PVA (PVA foam; Cook, Bloomington, IN) as a conventional particulate agent and tris-acryl gelatin microspheres (Embosphere Microspheres; Biosphere Medical, Rockland, MA) (EM) as a current spherical agent.

PVA is the permanent particulate embolic agent most widely used. It is ground from blocks of foam and then separated into different sizes to meet specifications. Each vial of 1 ml of PVA was diluted in a mixture of 10 ml of

50% sodium meglumine ioxaglate 320 mgI/ml (Hexabrix320; Tanabe, Osaka, Japan) and 50% saline.

EM are precisely calibrated, spherical, hydrophilic, micro-porous beads made of tris-acryl co-polymer coated with gelatin. They are inert translucent spheres that have demonstrated biocompatibility.[4] Each vial of 1 ml EM was diluted with a mixture of 10 ml of 50% sodium meglumine ioxaglate 320 mgI/ml and 50% saline.

SAP-MS was developed by Shinichi Hori,[7] and has not yet been approved by the Ministry of Health and Welfare of Japan or the Food and Drug Administration of the United States. It is a non-toxic solid particle of spherical shape. The particle size is calibrated in approximately 50-micron increments ranging from 53 to 350 microns (53-106, 106-150, 150-212, 212-250, 250-300, and 300-350 microns). SAP-MS has the properties of absorbing fluids and swelling within several minutes. Its diameters in an ionic contrast material, sodium meglumine ioxaglate 320 mgI/ml, and human serum are approximately 2 and 3.5 times larger than its original size in the dry state, respectively. The swollen particle, after absorbing fluids, is soft and compressible, but it maintains its spherical shape. SAP-MS is suspended in sodium meglumine ioxaglate 320 mgI/ml at a concentration of 10 mg/ml prior to injection according to our previous clinical experience.[5,6]

Embolization techniques and follow-up

The study protocol was approved by the Animal Experimentation Committee, and the experiments were performed according to the Animal Care Guidelines of our institution. Nine Japanese white rabbits weighing between 2.5 and 3.0 kg (mean 2.7 kg), divided equally into three groups, received three embolic agents of comparable particle size. Group I rabbits received PVA 180-300 μm, group II rabbits received EM 100-300 μm, and group III rabbits received SAP-MS 106-150 μm, which is equivalent to approximately 200-300 μm in suspension prior to delivery.

Each rabbit was anesthetized by intramuscular injection of ketamine hydrochloride (25 mg/kg, Ketalar 50; Sankyo Co., Ltd., Tokyo, Japan) and medetomisine chloride (0.1 mg/kg, Dormitor; Orion Corp., Espoo, Finland). The right femoral artery was surgically exposed, and an 18 G cannula was inserted with a hemostatic valve (Radifocus hemostasis valve II; Terumo, Tokyo, Japan) fixed on it. A 2.3 F microcatheter (Rapidtransit; Johnson & Johnson, Miami, FL) was inserted in the trunk of the right renal artery, and a preembolization renal arteriogram was obtained with manual injection of 2 ml of Hexabrix320. Each embolic agent was injected slowly using a 1 ml Luer-lock syringe until renal blood flow cessation under fluoroscopy. Immediate postembolization angiograms were obtained after 10 minutes. One-week later, follow-up angiogram was performed in the same manner, followed by dissecting the right kidneys after scarifying the animals with an overdose of pentobarbital injected into the abdominal aorta. The kidneys were fixed in 10% formaldehyde solution, processed, embedded in paraffin, and examined histologically at the median coronal section. Hematoxylin-eosin (HE) stain was used as a basic dye for cellular components, and elastica-van Gieson (EVG) stain was used to outline the arterial elastic fibers by light microscopy. The distribution pattern, shape and appearance, and associated perivascular reaction of each embolic agent were evaluated. In groups II and III, 10 peripheral occlusion points were randomly selected for each kidney section, and the short-axis diameters of a total of 30 particles were measured to compare the particle size range of EM and SAP-MS in the vessel lumen.

Results

Angiographic results

All embolizations were successfully performed in all groups. Injection of PVA particles was associated with particle accumulation in the microcatheter-hub in all procedures, while both EM and SAP-MS microspheres passed easily through the microcatheter without clumping.

All immediate angiograms of group I showed opacification at the renal hilum and homogenous parenchymal staining in the periphery of the kidney, representing the proximal occlusion level of PVA particles (Fig. 1). On the other hand, the angiograms of both groups II and III showed faint patchy inhomogeneous parenchymal staining immediately after embolization (Fig. 2).

All one-week follow-up angiograms showed complete occlusion of the main renal artery without recanalization or parenchymal visualization regardless of the embolic agent.

Histologic results

The histologic findings are summarized in the Table 1.

Coagulative necrosis was detected in most parts of the renal parenchyma, without significant differences between groups. No arterial wall rupture or subsequent hemorrhage was caused by the embolic agents in any of the groups.

In group I, the shape of PVA particles was irregular, and thrombi formed among particles. Although the thrombi were associated with infiltration of inflammatory cells consisting of neutrophils and macrophages,

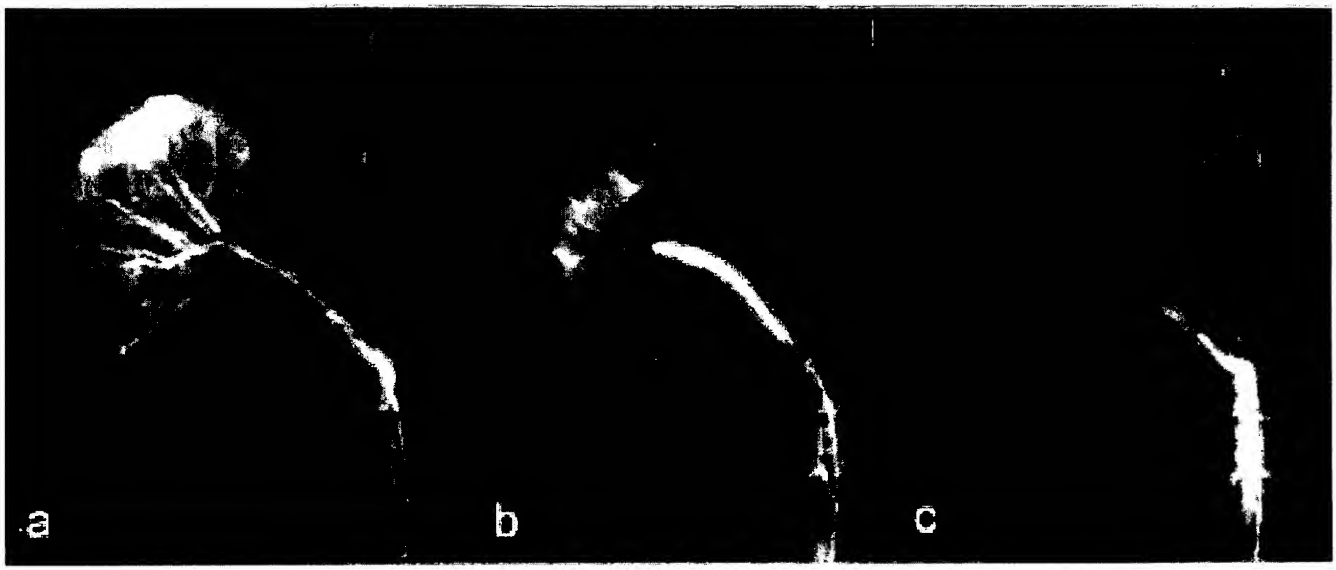

Fig. 1. Selective right renal angiogram of group I before (a), immediately after (b), and one week after (c) embolization with PVA. Hilar opacification with renal artery occlusion was seen immediately after embolization (b) and total occlusion of the renal artery without nephrogram after one week (c).

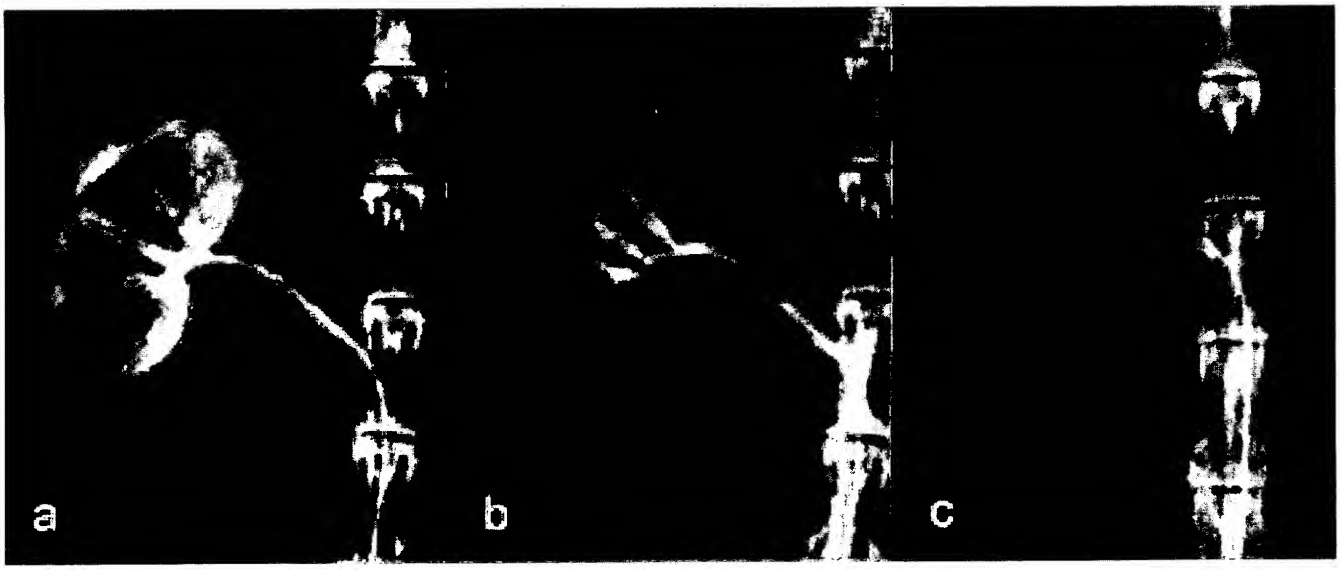

Fig. 2. Selective renal angiography of group III before (a), immediately after (b), and one week after (c) embolization with SAP-MS. Patchy inhomogeneous nephrogram was seen immediately after embolization (b) and the renal artery stump after one week (c).

no inflammatory reaction was observed in the vessel wall. The wall structures of vessels appeared to be preserved as examined by EVG staining. The renal artery was mostly occluded proximally between the main renal and segmental arteries, but a few isolated particles were seen at the level between the segmental and arcuate arteries (Fig. 3). Furthermore, tiny fragments of less than 100 μm migrated to the portion near or in the glomeruli (Fig. 4).

In group II, EM particles were clearly seen as a round eosinophilic substance with a peripheral basophilic rim corresponding to the gelatin coat. In the vessel lumen, EM particles constantly maintained their round shape, resulting in spaces among particles (Fig. 5). In the renal cortex with complete infarction, no perivascular reaction was seen around the particles, probably due to an absence of reactive activity. In the renal cortex with incomplete infarction, mild foreign body reactions to EM particles were seen to consist of macrophages predominantly and lymphocytes occasionally (Fig. 6). In vessel walls with

Table 1. Summary of the histological results

Group/Embolic agent	I. PVA	II. EM	III. SAP-MS
Size range (μm)	180-300	100-300	106-150
Occlusion level	Main-segmental artery	Arcuate-interlobular artery	Arcuate-interlobular artery
Mean short-axis diameter (μm)	N.A.	157 (100-230)	367 (190-550)
Fragments	Tiny-around glomerus	None	None
Shape	Irregular	Round	Swollen, deformed
Occlusion pattern	Aggregation with thrombus	Spaces among particles	No spaces among particles
Perivascular reaction			
Cellularity	None	Macrophages>lymphocytes	Macrophages
Internal elastic membrane	Preserved	Fragmented or disappeared	Fragmented or disappeared

PVA: polyvinyl alcohol
EM: tris-acryl gelatin microsphere
SAP-MS: superabsorbent polymer microsphere
N.A.: not applicable

Fig. 3. Group I. The arcuate artery was occluded by a PVA particle and thrombus formation. Note a single irregular-shaped particle does not occupy the whole vessel lumen. The arterial wall structure was well preserved without perivascular reaction. The surrounding renal parenchyma shows coagulative necrosis (EV stain, ×100).

Fig. 4. Group I. Unexpected tiny PVA fragments (arrows) migrated into or near the glomeruli (EV stain, ×200).

these reactions, the internal elastic membrane (IEM) was variably fragmented or lost. Some macrophages infiltrated into the gelatin-coated layer of EM particles. The short-axis diameter of EM particles at the occlusion point ranged from 100 to 230 μm, with a mean diameter of 157 μm. This tended to be within the injected particle size range (100-300 μm). EM particles traveled distally into the level of the arcuate to interlobular arteries, and distributed homogenously and uniformly through the section. At the level between the interlobar and segmental arteries, they crowded proximal to the level of distal occlusion.

In group III, SAP-MS particles were seen as a basophilic substance without membranous structure, and they contained multiple pores corresponding to the gas mixed during the manufacturing process. Compared with EM particles, SAP-MS particles did not reach more distally in the interlobular artery level. At the occlusion point, each single SAP-MS particle filled the cross-sectional vessel lumen tightly. In contrast to EM particles, swollen SAP-MS particles were markedly deformed and conformed to the vessel lumen without spaces among particles (Fig. 7). SAP-MS particles were closely apposed to the vessel wall and appeared to be in continuity with it. The vessel wall was circumferentially stretched with varying degrees of IEM thinning due to contact with the particles. In the renal cortex with incomplete infarction, mild foreign body reaction to SAP-MS particles was detected, and macrophages

Fig. 5. Group II. Embosphere particles occluded the interlobular artery in the infracted renal cortex. Each particle maintained the round shape and occupied the vessel lumen with spaces among particles. No perivascular reaction was seen around the particles (HE stain, ×40).

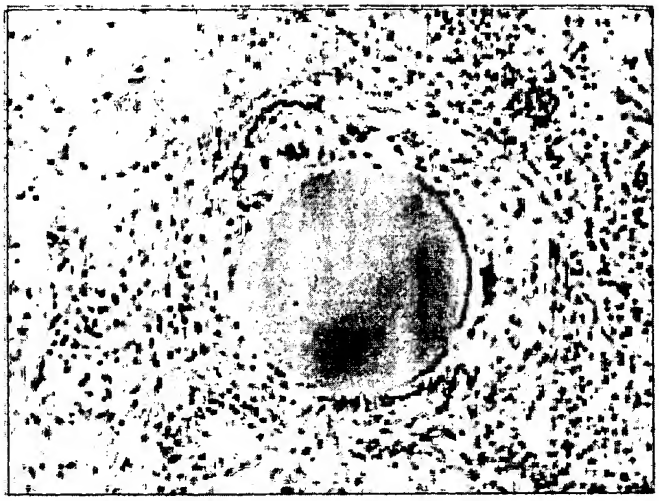

Fig. 6. Group II. An Embosphere particle occluded the interlobular artery in the renal cortex with incomplete infraction. The arterial wall structure was obscure and the internal elastic membrane was fragmented owing to the perivascular reaction. Single- or multinucleated macrophages were seen around the particle, and the gelatin-coat layer of the particle was partially infiltrated. Lymphocyte infiltration was also seen in the surrounding renal parenchyma (EV stain, ×200).

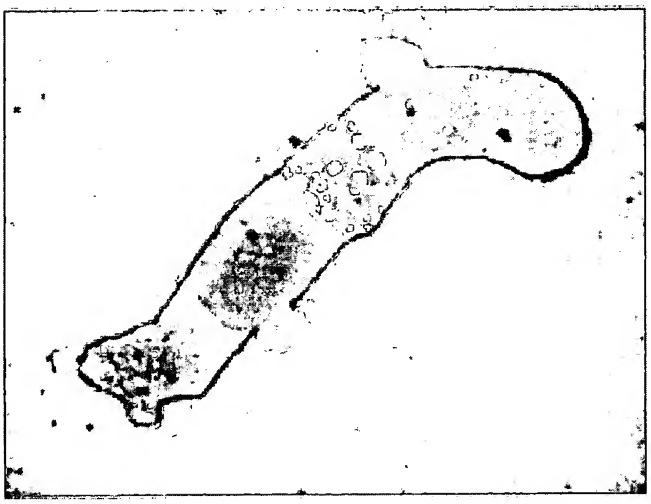

Fig. 7. Group III. The arcuate to interlobular artery was occluded with SAP-MS particles. The swollen particles were markedly deformed and conformed to the vessel lumen without space left. The particles contained multiple pores in various sizes. The internal elastic membrane was preserved and stretched along the whole vessel. The surrounding renal parenchyma showed coagulative necrosis (EV stain, ×40).

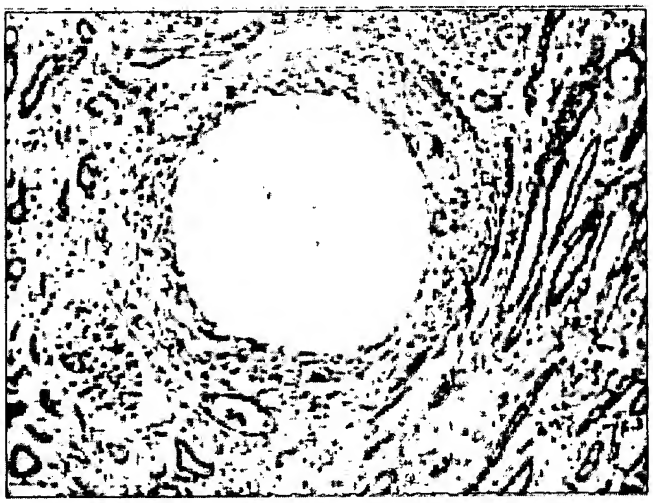

Fig. 8. Group III. An SAP-MS particle occluded an interlobular artery in the area with incomplete renal cortical infarction. The vessel wall structure was obscure and the surface of the particle showed irregularity because of mild perivascular reaction consisting of macrophages (HE stain, ×100).

infiltrated into the surface of SAP-MS particles (Fig. 8). IEM was fragmented or lost around the SAP-MS particles, as observed in the case of EM particles. The degree of such perivascular reaction was not significantly different between EM and SAP-MS particles. The short-axis diameter of SAP-MS particles at the occlusion point ranged from 190 to 550 μm with a mean diameter of 367 μm. This tended to be larger than the estimated particle size range injected (approximately 200-300 μm).

Discussion

PVA particles are generally irregular in shape, which results in unpredictable proximal vascular occlusion.[1,9-14]

In our study, the hilar opacification on immediate angiogram represented PVA particle accumulation between the main renal and segmental arteries. A determined range of regular PVA particle size was used, but tiny fragments reaching the capillary level were noticed in all kidneys. The significant risk of these unexpected fragments has been mentioned previously,[12] including the risk of distal and non-target embolization.

On the other hand, spherical embolic agents allow accurate grading and optimal geometric distal vessel occlusion.[15] Experimental studies have also demonstrated that spherical particles are more effective than others in achieving targeted vascular occlusion.[16,17] Both EM and SAP-MS have similar properties in that they are calibrated microspheres with smooth hydrophilic surfaces. They can be delivered easily through a microcatheter without clumping, and travel distally in the vessels.[5-7,18]

According to the *in vitro* and clinical studies, EM penetrates more deeply into the vasculature than PVA particles and can be injected with less difficulty.[16,18-20] They lead to more effective blockage of the blood supply, as they reach vessels of their own size and may reduce the possibility of blocking non-targeted vessels.

Although we used similar actual particle sizes, there was a remarkable difference in the degree of particulate penetration between PVA and both microspheres. However, these observations are similar to those of previous studies.[20]

Both EM and SAP-MS confine to the vascular lumen. EM specimens showed spaces left among particles, whereas SAP-MS showed no spaces left because it swells, deforms, and conforms to the vessel wall and other particles in the vessel. As the mean diameter of SAP-MS particles on cut section was larger than the injected size, we postulated that further swelling occurs *in vivo* after delivery. It expands gradually and stretches the arterial wall, leading to adequate, permanent occlusion of the vessels. The higher elastic property of SAP-MS particles is evidenced by their deformation according to the shape of the vessel lumen while maintaining their mechanical properties. This deformation does not affect the homogenous distribution of diameter size. This difference between EM and SAP-MS is probably caused by the different mechanical properties of the two materials in terms of surface structure, ability to swell, and deformability. SAP-MS particles maintained their mechanical integrity, and there was no evidence of particle fragmentation, arterial wall rupture, or extravascular migration of the particles caused by the swelling of SAP-MS particles after delivery. Their tendency to travel into vessels with diameters approximating their own and to swell later with no spaces among them may lead to tight occlusion of the vessel lumen without distal or proximal migration. This ability of swelling with significant deformability will make SAP-MS clinically suitable for embolization, especially occlusion of peripheral arteriovenous shunting.

The perivascular reaction to both EM and SAP-MS was similar. The mild foreign body reaction mainly consisted of macrophages and occasional lymphocytes, and it was associated with a variable degree of IEM disintegration. However, there was no evidence of actual vessel wall disruption. The vessel wall reaction might be due to the mechanical stretching or radial force of particle to vessel wall. Further investigations with long-term follow-up are needed regarding these changes and their clinical relevance.

In conclusion, SAP-MS resulted in a similar degree of targeted end-organ infarction after renal artery embolization as EM and PVA. Both EM and SAP-MS distributed homogenously in the distal vessels with mild perivascular reactions. SAP-MS is more deformable and conformable with the vessel lumen than EM. Further investigation with long-term follow-up is needed to determine the pathologic and clinical implications.

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膵動静脈奇形の1例
高吸水ポリマー（SAP-Microsphere）による塞栓術

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はじめに

膵の動静脈奇形（AVM）は希な疾患であり，本邦で42例が報告されている。治療法は外科的な完全切除であるが[1-4]，患者の全身状態やAVMの大きさ，存在部位により塞栓術が選択される場合もある[5-7]。

今回我々は，切除不能なdiffuse typeのAVMを経験し，放射線療法も不可能であったため塞栓術を施行した。塞栓時には最近開発されたSAP-Microsphereを用い，その有用性について術後の経過，および剖検での組織学的変化の検討を行った。

1．症　例

症例は60歳，男性。

主訴：吐血。

既往歴：58歳胃潰瘍，内服にて治癒。

家族歴：特記すべき事なし。

現病歴：1996年の4月頃より全身倦怠感，腹部膨満感があり近医受診，腹水に対し利尿剤の投与を受けた。経過観察中，同年の5月に吐血し緊急入院となった。

入院時現症：顔面蒼白で，腹部は膨隆し波動を認めた。腹壁表在静脈の拡張，くも状血管拡張は認めなかった。

入院時検査所見：白血球13,500，赤血球361万，ヘモグロビン10.3，ヘマトクリット30.3，BUN 101，CRTN 3.2，CRP 1.69，肝逸脱酵素およびビリルビン値は正常範囲内であった。

2．入院後の経過および画像所見

本症例は大量腹水と食道静脈瘤の破裂によって発症し，生化学的検査でも画像上も明らかな肝硬変の所見は認められなかった。超音波検査にて，大量の腹水と著明に拡張した脾静脈，膵頭部の拡大した血管群を認めAVMが疑われた。その確定診断のため血管造影が施行された。初回の腹腔動脈造影では拡張した左胃動脈，背側膵動脈，大膵動脈を認め，これらの血管を流入動脈とする豊富なナイダスを有するAVMが膵体部から尾部にかけて認められた（図1A）。動脈相早期より門脈および脾静脈の早期描出を認め，静脈相では造影剤の上腸間膜静脈，下腸間膜静脈への逆流を認めた。上腸間膜動脈造影でも拡張した下膵胃十二指腸動脈を中心に膵頭部にナイダスを認めた（図1B）。以上の所見より，膵のdiffuse AVMによる門脈圧

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〔索引用語：膵，動静脈奇形，門脈圧亢進症，塞栓術〕

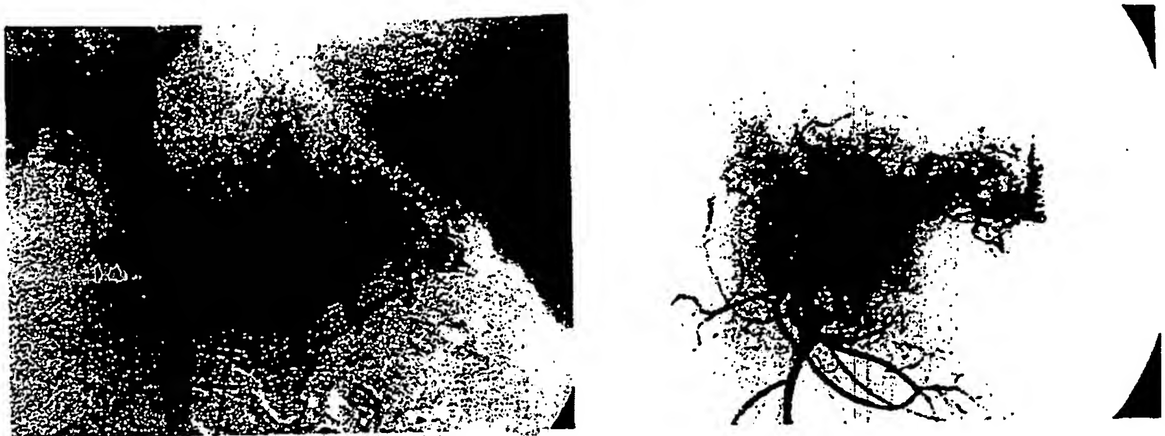

図1　動脈造影
A　腹腔動脈造影　膵体部から尾部のナイダスと脾静脈，門脈の早期描出を認める。造影剤の上腸間膜静脈（大→），下腸間膜静脈（→）への逆流を認める。B　上腸間膜動脈造影　拡張した横行膵動脈を流入動脈とするナイダスを膵頭部から尾部にかけて認める。

亢進が腹水や食道静脈瘤の原因であったと考えた。全身状態不良のため手術は考慮されず，腹水による腹厚増大のため放射線療法も施行不可能と判断された。患者本人および家族に，手術の適応がないことや放射線療法も困難なこと，従来の塞栓術では症状の改善を期待できないことを説明をし，今回の新しい塞栓物質の使用に対し同意を得た上で，治療計画をたてた。

3.　塞栓物質

super absorbent polymer microsphere：SAP-Microsphereは，アクリル酸ナトリウムとビニールアルコールとの共重合体で，塞栓物質の一つとして治験薬に承認されている。その水分を短時間に吸収し膨潤する性質を利用し，AVMに対する永久塞栓物質として応用されている。今回，使用したSAP-Microsphereは直径200～300mmで，血清中では平均3.47倍に膨潤する[8]。

リキッドコイル（Target Therapeutics社，Berenstein Liquid Coil）：極細プラチナコイルで，血流を利用してカテーテル先端より遠位の塞栓が可能である[9]。

4.　塞栓術および術後の経過

初回の塞栓術では，左胃動脈および背側膵動脈をSAP-Microsphereにて塞栓した。塞栓の方法は，最初SAP-Microsphereを用いて塞栓し，それでも塞栓が不十分と判断したときにliquid coilを追加した。1回目の塞栓術から1カ月後，2回目の塞栓術を施行した。左胃動脈と背側膵動脈および横行膵動脈からSAP-Microsphere，リキッドコイルを注入した。さらに1カ月後3回目の塞栓術を施行し，下膵十二指腸動脈より分枝する膵頭部ナイダスの流入動脈をSAP-Microsphere，リキッドコイルにて塞栓した。図2は1回目の塞栓術後から3カ月後の腹腔動脈造影である。初回の血管造影と比較しナイダスは減少しており，上腸間膜静脈や下腸間膜静脈への造影剤の逆流が消失している。このことから，塞栓術によるナイダス減少が門脈圧亢進症状を軽減したと考えた。この後，患者は転院し経過観察となったが，2カ月後に化膿性腹膜炎を併発し敗血症にて死亡した。感染の原因として，腹水除去のための留置チューブからの感染が考えられた。図3は，剖検時の膵の鏡検写真である。SAPはその特性通りに膨張しAVMの流入動脈レベル（血管経約0.6～1.0mm）を塞栓していた。また，肝内門脈にはSAP粒子を認めなかった。

5.　考　　察

膵臓の動静脈奇形は希な疾患である。本邦での報告例で重複なく42例を確認した。性別は，42例中7人が女性であった。本邦では欧米とは異な

図2　塞栓術後の
脾静脈へのシャ
下腸間膜静脈へ

Osler-Weber-
い[8,10]。臨
が多い
偶然発見さ
Chuangら
AVMから膵
管内への直
管粘膜の潰
胃静脈瘤から
中で，主訴と
一つはAVM
～3）の原因
瘤からの出
る出血の場
な症例が多
呈する症例
良で切除不
ような場合，
の適応とな
AVM症例で
したため側
減を維持で
の治療とし
位部を金属
一方で，ニ
症例は限ら

図2 塞栓術後の腹腔動脈造影
脾静脈へのシャントは残存したが，ナイダスの減少を得，下腸間膜静脈への造影剤の逆流は消失した。

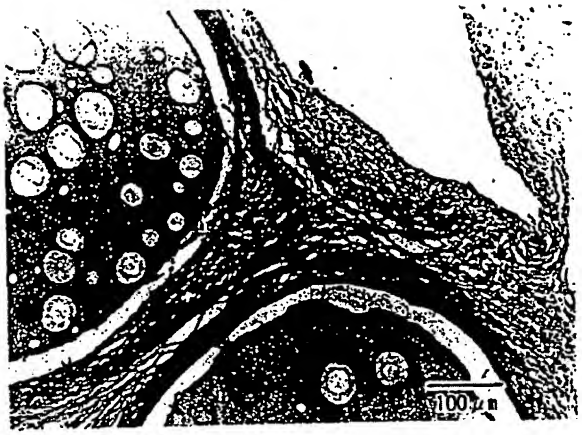

図3 脾のHE染色
SAP粒子は流入動脈レベルを塞栓し，流出静脈内には認められなかった。また，塞栓された血管壁には炎症細胞の浸潤はみられなかった。

Osler-Weber-Rendu病に合併するものは極めて少ない[1) 3) 10)]。臨床症状としては，消化管出血，腹痛が多い[3) 4) 10) 11)]。しかし，肝腫瘍の精査時などに偶然発見されることもある[11) 12)]。

Chuangらは，AVMが消化管出血の機序として1) AVMから膵管内への直接穿破，2) AVMから消化管内への直接穿破，3) AVMへの盗血による消化管粘膜の潰瘍形成，4) 門脈圧亢進症による食道胃静脈瘤からの出血を報告している[3)]。これらの中で，主訴となる出血は大きく2つに分けられる。一つはAVM，もしくはその近傍からの出血で1)～3) の原因による。もう一つは4) の食道胃静脈瘤からの出血である。過去の報告では，前者による出血の場合はAVM自体が小さく完全切除可能な症例が多かった[3) 4)]。しかし，門脈圧亢進症を呈する症例ではAVM自体が大きく，全身状態不良で切除不可能なものが報告されている[7)]。このような場合，放射線療法や経カテーテル的塞栓術の適応となる。塞栓術が施行された過去の膵AVM症例では，金属コイルを太い血管内に留置したため側副血行路が形成され，シャント量の軽減を維持できなかった[7)]。欧米では一般的なAVMの治療として，Ivalonで抹消部を塞栓した後に近位部を金属コイルで塞栓するという意見がある[5)]。一方で，エタノールによる塞栓術の報告もあるが症例は限られる[12)]。

今回の症例では，より細い血管を塞栓するために前述の塞栓物質を用いた。SAP粒子は造影剤を吸収後も透視下での確認はむずかしく，塞栓時に一部が脾動脈内に逸脱し脾梗塞を形成した。しかし，肝内門脈にはSAP粒子認めなかった。このことはSAP粒子はナイダスを通過せずAVMの塞栓に適した物質であったと考えられる。組織学的な検討では，塞栓したSAP粒子の血管壁に軽度の内膜の肥厚を認めたものの，炎症細胞浸潤はなく，組織の異物反応は極めて軽度であったと考えた。生体内でのSAP粒子に対する組織反応に関する報告はなく，今回の剖検結果はSAP-Microsphereの安全性を支持するものである。

ま と め

多くの流入動脈を持つ膵のdiffuse AVMにおいて，SAP-Microsphereやリキッドコイルを使用することにより，シャント量の低減を得ることができ臨床症状の改善を得た。

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Summary

Transcatheterial embolization of AVM in pancreas

Pancreatic arteriovenous malformation is a rare disease. Cases with portal hypertension used to have poor prognosis，but one was controlled by transcatheterial embolization using new embolic materials；SAP-microshere and Liquid coil. These materials can reach close to niduses but never pass through them.

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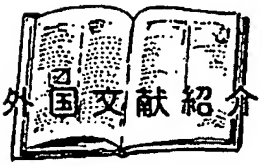

糖尿病の腎移植症例に生じた肺毛菌症
Pulmonary Mucormycosis in Diabetic Renal Allograft Recipients

Latif S et al
Am J Kidney Dis 29：461-464，1997

肺毛菌症は，真菌の一種である毛カビによって生ずるまれな日和見感染症であるが，このカビは，血管系に浸潤して血行性播種をきたしやすく，死亡率が高い。そのため，生検等による早期診断と適切かつ積極的な治療を行う必要がある。本疾患に罹患しやすい危険因子としては，長期にわたる好中球減少，糖尿病，免疫抑制剤の投与等があげられる。筆者らは，糖尿病の腎移植症例に生じた肺毛菌症を報告しているが，アンホテリシンBの投与と病巣の外科的切除により，治療に成功している。CTスキャンは，本症における肺の空洞性病変の構造を明瞭に描出するとともに，治療効果を評価する上で有用であった。

（瀬戸一彦）

臨床放射線

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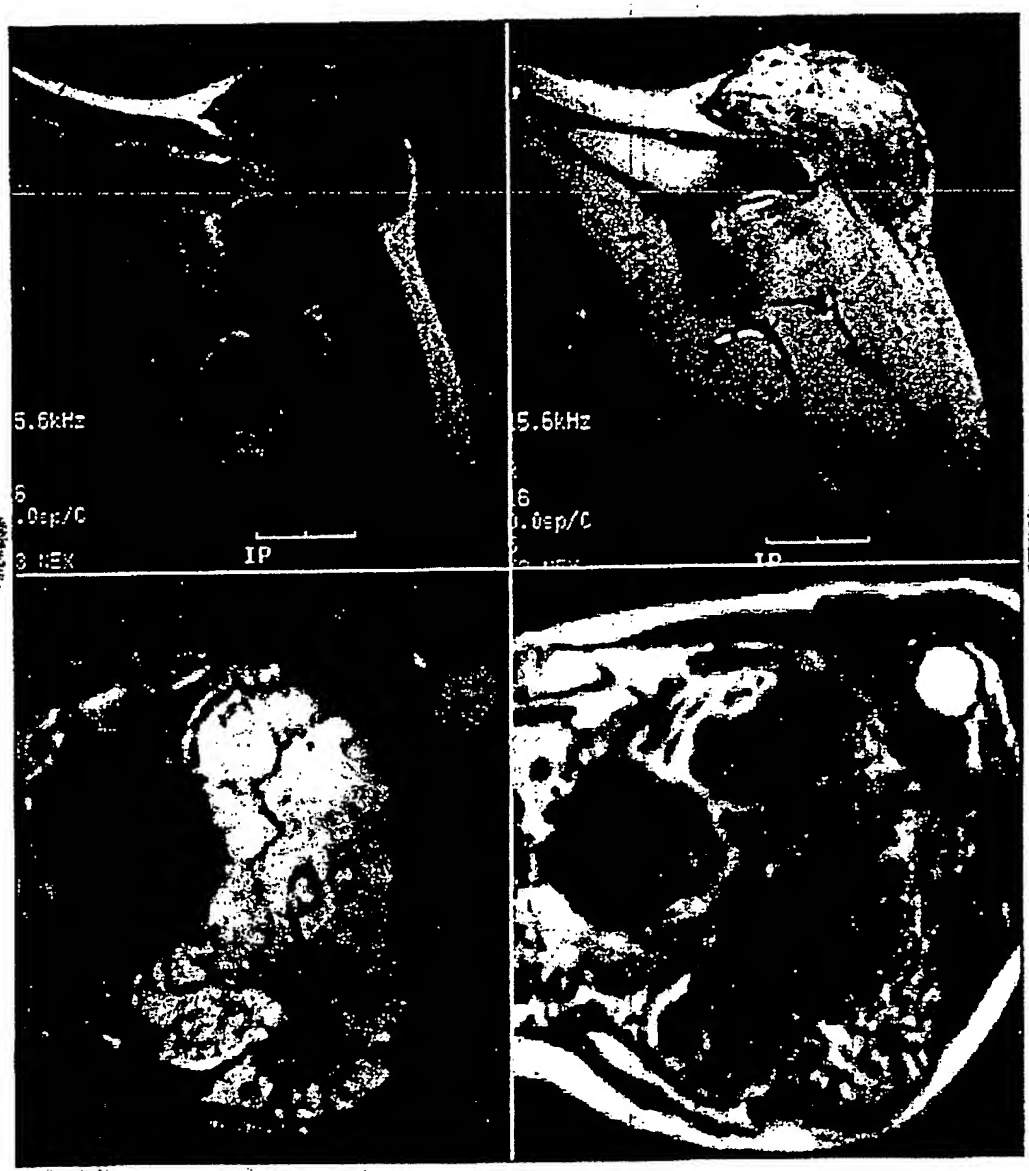

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A new deflectable superelastic cannula for percutaneous interventions: the «Smart Guide»

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Purpose: Percutaneous punctures have a limited degree of freedom; during percutaneous laser decompression of intervertebral discs, for example, only translation and rotation are possible. Our purpose was to increase the degree of freedom of the functional end of the cannula to facilitate the access to important structures and increase the accessible volume.
Materials and Methods: Different materials (nitinol, steel) have been tested in vitro on phantoms from animal tissues and organs. Subsequent to animal cadaver ex vivo experiments (pig and oxtail) and production by (Daum, Schwerin, Germany) the deflectable cannula was used in ten CT-guided laser decompressions (six medio lateral herniations of L4-L5 and four L5-S1) after informed written consent from the patients. The accessible volume and the laser ablation size have been evaluated and compared with disc decompression performed with the standard cannula. All patients underwent a previous MRI of the spine, repeated 30 minutes after intervention and 6 weeks after, together with a neurological examination after 3 and 6 weeks.
Results: The best results were achieved with a nitinol tube holded in an outer sleeve which, on protrusion, it recovers its previous curvature of 90° of 15 mm radius curvature (18 gauge). The access to the intraspinal disc was facilitated and the cannula could be placed directly into the center. The volume of laser ablation in the disc can be increased of about 100%. Despite one bleeding which required no additional treatment, no complication occurred.
Conclusions: Deflectable interventional cannulæ can be made from superelastic nitinol. The deflection of the distal end facilitates access, helps to prevent injuries of important structures and increases the volume of laser ablation. Further improvement of the deflectable needle is required in terms of an easier control of its degree and orientation.

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Laser decompression of herniated lumbar intervertebral discs under MRI-guidance

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Purpose: CT-guided laser decompression is an established treatment for contained disc herniation. Since MR allows multiplanar slice orientation, display of thermal changes and water content of the intervertebral disk without ionising radiation, we have developed MR-guided laser decompression.
Materials and Methods: Subsequent to animal (oxtail) and human cadaver feasibility studies of MRI laser application, sequences, slice orientation and patient position within a horizontal open 0.2 Tesla MRI unit was worked out on volunteers. In six patients, three men and three women, suffering from sciatica, with previous spinal MRI and proven contained disc herniation (four at the level L4-L5 and two at L5-S1), disc decompression was performed in lateral prone position. Imaging of the disc and the trajectory planning were performed prior to local anesthesia and insertion of an 18-Gauge titanium cannula (Daum, Schwerin, Germany). Puncture of the discs was performed under control of 12-sec. breathhold gradient echo sequences in transverse sagittal and coronal orientations. The laser process was controlled by gradient echos. Post-interventional examinations of Lasegue's sign and subjective sensation of the patient were used for the documentation of results. All patients underwent neurological examination after 3 and 6 weeks and a spinal MRI was performed after 6 weeks.
Results: The procedure was successfully completed in all patients. Localization of the needle position and placement within the spinal disc was possible. In addition to a moderate pain, no other complications occurred. The use of shifted-echo gradient echo provides the display of thermal changes. An improvement of up to 80% of reduction of symptoms was reported.
Conclusions: Laser decompression of lumbar spinal discs herniation under MR is feasible but slice positioning and temperature mapping, in particular, require further improvement. Opto-electronic navigation for interactive slice orientation and PC post-processing of temperature images are currently under development.

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Management of advanced pelvic bone tumors by transarterial embolotherapy using SAP-Microspheres. A preliminary report

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Purpose: To evaluate the effectiveness of transarterial embolotherapy in advanced pelvic bone tumors using superabsorbent polymer microspheres (SAP-MS, sodium acrylate and vynil alcohol copolymer).
Materials and Methods: SAP-MS is a spherical permanent embolic material which can tightly occlude a vessel lumen by swelling after absorbing serum within 5-10 minutes. The size of the particle can be selected in 50 micrometer steps. Between January 1996 and December 1998, five inoperable hypervascular pelvic bone tumors over 10 cm in diameter (M:F=2:3; mean age = 62.9; metastases 3 [RCC 1, ureteral ca. 1, thyroid ca. 1], giant cell tumor 1, osteosarcoma 1) were embolized transarterially in several sessions to improve the patients' daily life activities (DLA). All patients had uncontrollable skeletal pain. In three patients, chemotherapy or immunotherapy were not successful before TAE. SAP-MS (50-250 micrometer) mixed with ionic contrast material (Hexabrix 320) were injected through the microcatheter placed in each feeding artery. No antineoplastic agent was used in TAE. In all patients, dynamic MRI or CECT was performed before and after TAE to evaluate the embolic effects to the tumors.
Results: Improvement of the DLA with pain relief was obtained in all patients without combined therapies. A reduction in the tumor size with necrotic changes was observed in three patients at MRI or CT follow-up. No serious complications were found such as skin or muscle necrosis or peripheral neuropathy except for a small skin ulcer in a case with metastatic ureteral cancer.
Conclusions: TAE using SAP-MS for advanced pelvic bone tumors effectively contributed to the improvement of patients' DLA.

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Diagnostic and therapeutic breast interventions using the new digital stereotactic breast puncture system Mammotome™

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Purpose: The new digital stereotactic breast puncture system Mammotome™ provides a minimal invasive procedure for the removal of mammographically suspicious lesions and promises a new approach for the diagnosis and therapy of breast lesions. Our study was designed to evaluate this method with particular respect to resection of focal lesions.
Materials and Methods: Between July 1998 und January 1999, we have performed 83 stereotactic breast interventions in 90 patients with mammographically suspicious lesions (ACR 2, 3 and 4) using the Mammotome™ system. In seven cases, the puncture could not be performed because the lesions, identified by conventional film mammography, were not visualized by the Mammotome™ digital imaging system. All interventions were performed in prone position using an 11-G needle and local anesthesia. In case of focal lesions, a complete resection was attempted, whereas in case of diffuse lesions, we pursued the acquisition of representative tissue samples. After the intervention, a conventional film mammography was performed as well as radiography of the acquired specimen.
Results: Before intervention focal (46) or diffuse (37) lesions were rated as ACR 2 (six cases), ACR 3 (53) and ACR 4 (24). In 68 cases the lesion diameter was 2 cm or less. Reason for the intervention was microcalcification (64) and/or suspicious dense tissue (39) or derangement of the tissue structure (4). In focal (resp. diffuse) lesions, 27 (resp. 5) complete resections and 19 (resp. 32) representative tissue samples were acquired. In two cases the intervention had to be stopped because of bleeding.
Conclusions: The digital stereotactic puncture system Mammotome™ is useful for a safe and fast acquisition of representative tissue samples. A complete resection of focal lesions is however possible in 60% of cases only. This system is therefore a useful diagnostic but not a therapeutic device.

le superelastic cannula for percutaneous : «Smart Guide»

:el, A. Winkel, W. Triebe, R. Seibel
:iagnostic and Interventional Radiology, University Tülheim/Ruhr, Germany

:ous punctures have a limited degree of freedom; is laser decompression of intervertebral discs, for lation and rotation are possible. Our purpose was :e of freedom of the functional end of the cannula :cess to important structures and increase the

hods: Different materials (nitinol, steel) have been ı phantoms from animal tissues and organs. nal cadaver ex vivo experiments (pig and oxtail) (Daum, Schwerin, Germany) the deflectable can- ı CT-guided laser decompressions (six medio late- 4-L5 and four L5-S1) after informed written con- nts. The accessible volume and the laser ablation ıated and compared with disc decompression per- ındard cannula. All patients underwent a previous :peated 30 minutes after intervention and 6 weeks a neurological examination after 3 and 6 weeks. esults were achieved with a nitinol tube holded in :h, on protrusion, it recovers its previous curvature radius curvature (18 gauge). The access to the is facilitated and the cannula could be placed nter. The volume of laser ablation in the disc can ıt 100%. Despite one bleeding which required no it, no complication occurred.

:ctable interventional cannulæ can be made from The deflection of the distal end facilitates access, ijuries of important structures and increases the)lation. Further improvement of the deflectable ı terms of an easier control of its degree and orien-

ssion of herniated lumbar intervertebral -guidance

sch, R. Seibel
)iagnostic and Interventional Radiology, University Tülheim/Ruhr, Germany

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研究速報

高吸水性樹脂による肝区域動脈塞栓術の試み

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井上　悦男[1]　堀　　信一[1]　鳴海　善文[1]
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Experimental Studies of Segmental Hepatic Artery Embolization with a Super Absorbent Embolic Agnet

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Research Code No. : 514.4

Key Words : Embolization, Embolic material, Liver tumors

Super absorbent (Sumikagel®) is a unique polymer mainly composed of polysodium acrylate (PSA). When PSA contacts water, it absorbs water and swells in a few seconds. This new embolic material suspended in Lipiodol (Lp-PSA), was used for hepatic artery embolization in five dogs. The purpose of this study is to examine the necrotizing effect of the new embolic material on segmental hepatic artery embolization. Gross liver examination demonstrated congestion and segmental infarction within the embolized area, and microscopically focal necrosis of liver parenchyma was observed. Segmental hepatic artery embolization with Lp-PSA should be an effective method of hepatic tumor embolization.

はじめに

従来の肝動脈塞栓術では，腫瘍生存部が残存するために周囲肝実質も含めた壊死効果をもつ塞栓術の必要性が言われてきた．今回，高吸水性ポリマーの一つであるアクリル酸ソーダ重合体の瞬間的な吸水膨潤性に着目し，Lipiodolを分散媒とした懸濁液を作製した．これを用い実験的に肝区域動脈塞栓術を行い塞栓された肝区域の壊死を確認した．そこで我々は，この新しい塞栓物質を用いることで優れた動脈塞栓効果が期待できると考え報告する．

I．新塞栓材料について

使用した高吸水性ポリマー[1]は，アクリル酸ソーダ重合体（Sumikagel®，N-1010）で，粒径10～20μmの無定形白色粉末である（Fig. 1）．

このポリマーは，ほぼ瞬間的に水を吸収し，5～10分で吸水量は最大に達する．純水で1,000倍，生理食塩水で80～100倍の吸水能力を有する．吸水後はゲル状となる．更に，このポリマーは水に溶解せず，毒性は無く，また抗原性を有しない．我々は高吸水性ポリマーを分散相，Lipiodolを分散媒とする懸濁液を作製した．高吸水性ポリマーはLipiodolと共に血管内を流れ，動脈末梢で吸水，直径を増して塞栓物質として作用するものである．懸濁液の濃度は高吸水性ポリマー10mg/Lipiodol 1mlであり，塞栓術に使用したマイクロ

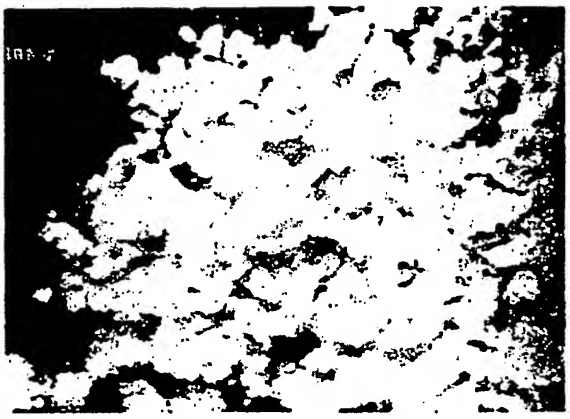


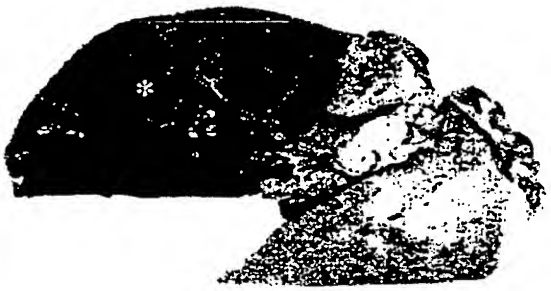
Fig. 1 The sample of white powder of polysodium acrylate (PSA).

カテーテル（内径0.45mm）を容易に通過した．Lipiodol との懸濁にて粒径，吸水能力に変化は無かった．

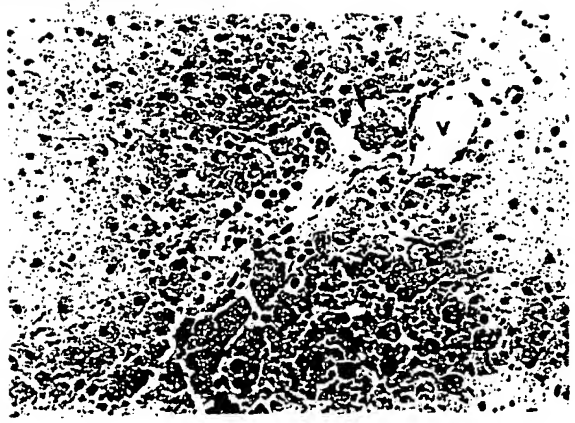
II. 成犬における肝区域動脈塞栓術の検討

雑種成犬6頭に対し，大腿動脈穿刺を行い肝区域動脈塞栓術を行なった（Fig.2a）．塞栓物質には高吸水性ポリマー，Lipiodol の懸濁液を用いカテーテル内で直接血液ないし生理食塩水と触れないように少量の Lipiodol を先行させ，透視下で血流が停止するまで注入した．Lipiodol，高吸水性ポリマーの使用量はそれぞれ0.1～0.25ml/kg，1.0～2.5mg/kg であった．1例は，control として

a



b



c

Fig. 2 a. Catheterization to the artery of the right anterior segment using a 2.5 F microcatheter. A catheter tip (arrow). b. Cut specimen of the dog liver embolized with a 0.2ml/kg Lipiodol (Lp)+1.0mg/kg PSA revealed a segment of infarction with congestion (*). c. Micrograph (H.E.)×100. 48 hours after Lp-PSA injection. Necrosis of hepatocyte and sinusoidal congestion were obserbed. PSA (arrows) within sinusoid. Central vein (V).

Lipiodol単独で0.25ml/kg使用した．24～48時間後4頭（controlを含む），4週後に2頭屠殺したのち，肝，肺を摘出し肉眼的及び組織学的検討を行った．塞栓領域の肝葉は肉眼的にうっ血様で明らかな境界をもった梗塞巣であり(Fig. 2b)，組織学的所見としてはうっ血像と巣状あるいは区域性の凝固壊死を認めた．また，類洞内に膨潤した高吸水性ポリマーを確認できた(Fig. 2c)．肺組織に肺梗塞による変化は指摘できなかった．一方，Lipiodol単独例では壊死巣は見られなかった．

考　察

通常の肝動脈塞栓術の限界として肝癌の増殖先端部や微小転移巣に対して効果が乏しいことが上げられる．その理由としてこれらの病巣が類洞を介して門脈血流を受けるためと言われている．最近，壊死効果を高めるために幾つかの手法を用いた肝区域動脈塞栓術[2)3)]が肝癌の治療法として注目をあびており，新しい塞栓物質，塞栓方法の開発が望まれている．今回の検討の結果から，この新塞栓物質は経動脈的使用により容易に肝実質を壊死に至らしめることができ，更に，肝区域動脈塞栓術の手法を用いて特定の区域のみを安全に塞栓することができると考えられた．グリソン鞘周囲の小血管にも一部高吸水性ポリマーを認めた部分があったが，類洞内に膨潤した高吸水性ポリマーを組織学的に確認できた．粒径10～20μmの高吸水性ポリマーが類洞内で水分を吸収することができたと考えられる．

今回，分散媒としてLipiodolをもちいたが，佐藤ら[4)]の報告では，成犬に0.2－5ml/kgのLipiodolを肝動脈から注入しても梗塞巣は見られなかったとしており，我々の検討でも，Lipiodol単独使用0.25mg/kgにて肝区域動脈塞栓術を行っても肝実質に変化はなかった．

以上の事から，高吸水性ポリマー自体が肝実質を梗塞に至らしめる能力をもつことが示唆され，肝区域動脈塞栓術の塞栓物質として有用であると思われる．また，摘出肺に高吸水性ポリマーを認めず梗塞巣も存在しなかったが，A-V shuntを伴う場合には慎重な使用が必要と考えられる．今後，臨床使用を含めさらに検討を加える予定である．

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